REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
05-10-2013		

4. TITLE AND SUBTITLE

Stochastic Modeling of the Persistence of HIV: Early Population Dynamics

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Naval Academy
Annapolis, MD 21402

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
Trident Scholar Report no. 420 (2013)

12. DISTRIBUTION / AVAILABILITY STATEMENT

This document has been approved for public release; its distribution is UNLIMITED.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

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15. SUBJECT TERMS
mathematical biology, stochastic differential equations, HIV, differential equations

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**		62	**19b. TELEPHONE NUMBER** *(include area code)*

U.S.N.A. — Trident Scholar project report; no. 420 (2013)

Stochastic Modeling of the Persistence of HIV: Early Population Dynamics

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Abstract

Mathematical modeling of biological systems is crucial to effectively and efficiently developing treatments for medical conditions that plague humanity. Systems of differential equations are the traditional tools used to theoretically describe the spread of disease within the body. In this project we consider the dynamics of the Human Immunodeficiency Virus (HIV) in vivo during the initial stages of infection. Both mathematical and biological results support the idea that contact with the HIV retrovirus does not automatically imply permanent infection. Given factors such as the CD4+ T-cell growth rate, infection rate, and viral clearance rate, it is possible to correctly predict the end viral state in a deterministic model. While this is useful, such a model lacks the randomness inherent in physical processes and parameter estimation. To account for this, our project examines both discrete and continuous stochastic models for the early stages of HIV infection. These models are crafted using the knowledge of biological interactions and fundamental mathematical principles. We also examine the well-known three-component deterministic model in greater detail, proving existence and uniqueness of the solutions. Furthermore, we prove that solutions remain biologically meaningful, i.e., are positivity preserving, and perform a thorough stability analysis for the equilibrium states of the system. Finally, we develop two new stochastic models and obtain extensive numerical results to measure the probability of infection given the transmission of the virus to a new individual. To simulate the dynamics of the virus, we employ a number of computational methods for ordinary and stochastic differential equations, including Runge-Kutta methods and the Euler-Maruyama scheme.

Keywords: mathematical biology, stochastic differential equations, HIV, differential equations.

Acknowledgments

This project required a tremendous amount of effort on my part, but even more so from the people who advised and supported me. I would like to thank first and foremost my advisers, Prof Raghupathi and Prof Pankavich, but also those from the Math Department at the Naval Academy who encouraged and developed me. A special shout out goes to Prof Alevras, Prof Lockhart, and Prof Popovici.

Thanks is also given to the Trident Committee, especially Prof Kidwell, for their support.

Finally, I owe a debt of gratitude to friends and family for their unending and unconditional help.

Contents

List of Figures

CHAPTER 1

Introduction

The human body has been studied for hundreds of years, and the knowledge accumulated to date includes the intricate molecular level mechanisms that determine how a virus infects cells and reproduces. This information is necessary to develop treatments for maladies ranging from Hepatitis to the Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS). An understanding of the accumulation of millions of these interactions across a timescale of medical relevance permits the creation of better treatment methods. As recently as fifty years ago, this could only be done via experiment and repeated trials. Today, through the advent of high speed computing, viral kinetics can be simulated using mathematical models. We can utilize our current understanding of molecular and cellular dynamics, describe them in mathematical terms, and simulate interactions within the body many thousands of times to examine the course of a virus from initial infection to a long-term steady state. In this particular project, we will derive a mathematical model of HIV infection within a single human host, examine it, simulate it, and improve upon it.

The general principle behind any sort of mathematical model is to examine closely the interactions between the quantities being analyzed. We begin with a small number of initial axioms, and then follow the implications of these axioms thoroughly to their conclusion. As a basis for our model, we use the general biological understanding of HIV dynamics that is widely-accepted and well studied. The following will be a brief non-technical discussion of the populations and interactions that impact the modeling of HIV within the body.

There are many biological operators involved in the interaction between HIV and cells within the human body. We deal with a small portion of these populations. The first group is a subset of the population of lymphocytes, which in turn are a type of white blood cell. This subset is known as CD4+ T-cells, or helper T-cells. These T-cells have a variety of functions, including secreting substances that stimulate the immune system, acting as memory agents for the immune system, and regulating the immune response. In short, CD4+ T-cells detect and direct immune system responses to invading bacteria and viruses. Without them, the body suffers from opportunistic infections that are greater in severity and duration than they would be if the CD4+ T-cells were otherwise not present. HIV, which refers in this case to the virus, not the disease or symptoms associated with it, is a retrovirus that infects helper T-cells. The virus, which is significantly smaller than the T-cell (120 nanometers in diameter compared with 7 micrometers in diameter), breaches the cell wall and transports its RNA into the T-cell nucleus, where it may remain dormant for a time. Upon activation, the T-cell ceases its function as part of the immune system and instead produces additional copies of HIV. These infected T-cells, along with the healthy T-cells and free floating HIV, are the populations with which we are concerned, and will appear within our mathematical model.

The second aspect of the model's creation involves incorporating the interactions between these populations and deriving their corresponding mathematical representation. For each population, we need only concern ourselves with the ways in which the population is increased and how members of this group are removed. Healthy T-cells are created from stem cells in the bone marrow, and mature in the thymus. While production of T-cells does decrease with the aging of the human body, it is considered constant in this project for two reasons. First, there is no method other than this production that can possibly affect T-cell creation, and second, the time scale of interest within the model is sufficiently small to consider the T-cell production rate as constant. When considering removal of these cells, we note that T-cells do age and, in time, die. Within the model, we assume that each T-cell lives for roughly the same amount of time, and

thus, the death rate does not vary over the entire population. Instead, the overall number of T-cells lost in a group over a certain period of time is proportional to the number of T-cells within the group. The other mechanism through which the population of healthy T-cells may decrease is through infection. In considering the effects of infection, we utilize an interaction term that arises from the widely-used "mass action principle" to describe the transfer which occurs between populations when the virus infects healthy T-cells. This mass action term represents the idea that the rate of interaction, or infection, is directly proportional to the product of the participating populations, namely those of virions (or virus particles) and healthy T-cells. This completes the interactions for the healthy T-cells. We note that the only way to add to the population of infected T-cells is for the HIV virus particle to physically infect healthy T-cells. Beyond this, there is no other way of creating an infected T-cell. Thus, in our mathematical model we can use the same mass action term to describe the removal of the healthy T-cells and the addition of infected T-cells. Similar to the healthy T-cells, infected T-cells die off or are cleared by the immune system at a rate proportional to the size of their current population. The virus, while produced from the infected T-cell, does not cause the destruction of the infected T-cell. Thus, we do not need to include such a transition within the model.

While the virus production rate does differ from cell to cell, we can assume that the aggregate rate is constantly proportional to the population of infected T-cells. This is the only mechanism by which the virus can be created. Contrastingly, there are two manners in which the virus can be removed, or cleared, from the body. The first is through viral infection of T-cells. The act of infecting a healthy T-cell must technically remove a virus particle from the population of viruses that can infect further T-cells. However, when considering the overall population quantities, the number and rate of viruses lost this way is minute compared to other methods of creation and destruction. Hence, we will omit this possibility from the model. The second method of removal is known as viral clearance. It is the removal by the body of individual virus particles, and is performed at a rate proportional to the current amount of virus particles within the body. With these interactions, we can construct differential equations that model the rates of change of these populations by utilizing the assumptions discussed above.

For all of the interactions we have described, the rates of change were proportional to a population. In the equations that follow, we endow each of these interactions with a proportionality constant, in the necessary units to guarantee that each term within the equation is measured in organisms (cells or virions) per unit time. For instance, the creation rate of the healthy T-cells will be represented by the constant $\lambda > 0$, whose unit of measurement is T-cells per unit time. Analogously, the rate coefficient for the creation of infected T-cells is measured in unites that are the inverse of virus particles multiplied by a unit of time. Thus, when we sum up the interactions for each population, we arrive at a growth rate. Mathematically, the rate of change of a quantity is given by its derivative, and hence a differential equation results. In our case, the system is known as the Three Component Model (3CM) [**16**].

Before stating the equations, we attach variable names to each of the populations under consideration. In the notation used, the population of healthy T-cells is denoted by T, the infected T-cells by I, the virus population by V, and the derivative of any population X with respect to time is indicated by $\frac{dX}{dt}$, as is standard. There are six different proportionality constants, given in the table below.

Coefficient	Relevant Biological Process	Mean Value	Units
λ	Healthy T-cell growth	0.1089	$\frac{cells}{day}$
μ	Healthy T-cell death	0.01089	$\frac{1}{day}$
k	Infection	1.179×10^{-3}	$\frac{1}{virions \times day}$
δ	Infected T-cell death	.3660	$\frac{1}{day}$
p	Virus production	1426.8	$\frac{virons}{cells \times day}$
c	Viral clearance	3.074	$\frac{1}{day}$

We note several important characteristics of these coefficients. Since the coefficients are taken from biological considerations, we assume that they are all nonnegative, and we fix their units such that the end result of each equation is ultimately represented in units of $\frac{cell}{time}$ or $\frac{virons}{time}$. The units for each T-cell population is simply "cells", while the units for the virus population is "virons".

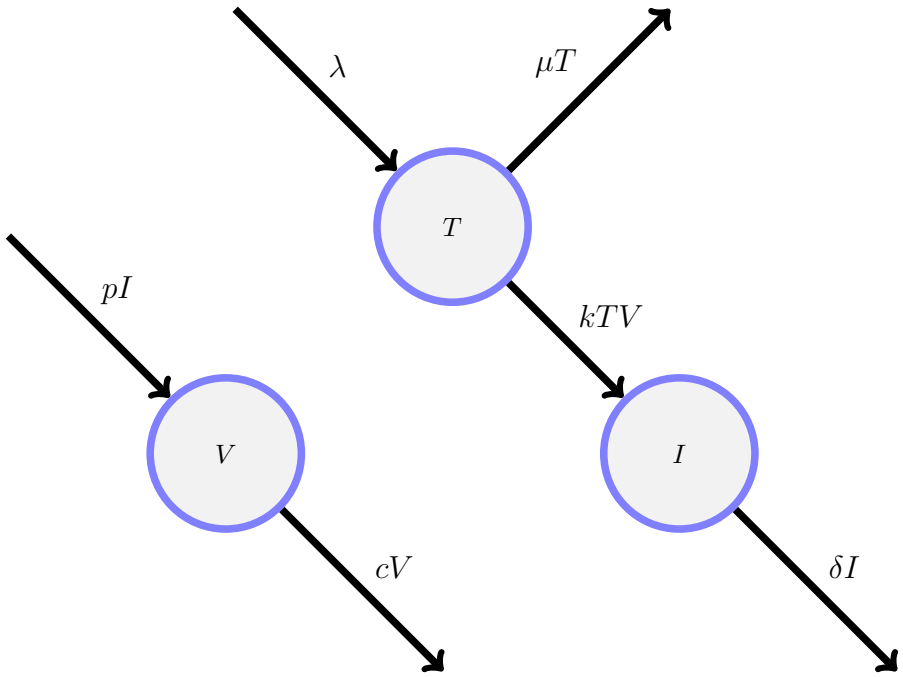


FIGURE 1.1. Illustration of 3CM

When we combine the multiple interactions that govern the change in population of the healthy T-cells, including their natural growth rate, natural death rate, and infection rate, we arrive at the differential equation

$$\frac{dT}{dt} = \lambda - \mu T - kTV. \tag{1}$$

This equation mathematically describes the biological interactions presented above. A similar equation is derived for the infected T-cells, namely

$$\frac{dI}{dt} = kTV - \delta I. \tag{2}$$

Here, it is important to note that the "kTV" terms in the first and second equations represent the same interaction and yield the same number of cells transferred from the healthy T-cell population to the infected T-cell population. This occurs because the transfer of cells between these populations occurs at a one to one ratio.

Next, we consider the rate of change of the virus population and derive the corresponding differential equation to represent its dynamics:

$$\frac{dV}{dt} = pI - cV. \tag{3}$$

The diagram (1) gives a visual representation of the differential equations. We see each of the populations within a circle, while the arrows running to and from each circle describe how they interact and change.

Of course, the unknown populations within these equations depend upon one another, and hence they are not examined independently. Just as the interaction of populations within the body serves to connect the behavior of virions and T-cells, the functions within the differential equations above are also coupled. They describe, for instance, the notion that an increase within the virus population will cause a similar increase

within the infected T-cell population. Because of these interactions, we study the equations together and look at properties of the system of three equations, rather than an isolated equation. Thus, the equations together are known as the "Three Component Model."

(3CM)
$$\begin{cases} \dfrac{dT}{dt} = \lambda - \mu T - kTV \\ \dfrac{dI}{dt} = kTV - \delta I \\ \dfrac{dV}{dt} = pI - cV. \end{cases}$$

CHAPTER 2

The Deterministic Three Component Model

2.1. Existence and Uniqueness of Solutions

The most fundamental step in examining the Three Component Model is to show that a solution to the initial-value problem does, in fact, exist, and that this solution is unique. To prove this, we utilize the classic theorem of Picard and Lindelöf, which is stated in [**3**].

THEOREM 2.1.1 (Picard-Lindelöf). *Let $n \in \mathbb{N}$ and $y_0 \in \mathbb{R}^n$ be given. Assume the function $f : \mathbb{R}^n \times \mathbb{R} \to \mathbb{R}^n$ is locally Lipschitz in its first argument and continuous in its second argument. Then there exist $t^* > 0$ and a unique function $y : [0, t^*] \to \mathbb{R}^n$ satisfying*

$$y'(t) = f(y(t), t)$$

for every $t \in [0, t^*]$ and the initial condition $y(0) = y_0$.

In the case of the three component model, we have:

$$y = \begin{bmatrix} T \\ I \\ V \end{bmatrix} \text{ and the autonomous system } f(y) = \begin{bmatrix} \lambda - \mu T - kTV \\ kTV - \delta I \\ pI - cV \end{bmatrix} \tag{4}$$

We note that since f has a continuous, bounded derivative on any compact subset of $\mathbb{R}^3$ that f is locally Lipschitz in y. Hence, by the Picard- Lindelöf Theorem, there exists a unique solution, $y(t)$, to the ordinary differential equation $y'(t) = f(y(t), t)$ on some time interval $[0, t^*]$.

2.2. Gronwall's Inequality and Applications to the Three Component Model

Gronwall's inequality is a tool of mathematical analysis that allows us to bound solutions of differential equations. In many cases, we cannot explicitly obtain formulas for solutions, so it must suffice to derive bounds on their growth. Gronwall's Inequality permits us to do just this.

2.2.1. Gronwall's Inequality.

THEOREM 2.2.1. *Let $[a, b]$ be an interval and f and g be continuous functions on $[a, b]$ with f differentiable on $[a, b]$. If f satisfies the differential inequality:*

$$\frac{df}{dt} = f'(t) \leq f(t)g(t) \tag{5}$$

for every $t \in [a, b]$ then

$$f(t) \leq f(a)e^{\int_a^t g(s)ds} \tag{6}$$

for every $t \in [a, b]$.

The proof to this theorem is well known, and can be found in [**6**].

2.2.2. Application to the Three Component Model.

THEOREM 2.2.2 (Boundedness and Positivity for the Deterministic Three Component Model). *Let $t_0 > 0$ be given. In the three component model, if the initial conditions satisfy $T(0) > 0$, $I(0) > 0$, and $V(0) > 0$, then for all $t \in [0, t_0], T(t), I(t)$, and $V(t)$ will be bounded and remain positive.*

PROOF. We assume that $T(t)$, $I(t)$, and $V(t)$ initially have positive values. From the previous theorem, there exists a t^* such that the solution exists on $[0, t^*]$.Let us denote by T^* the largest time t for which $T(t) > 0$, $I(t) > 0$, and $V(t) > 0$, or more precisely

$$T^* = \sup\{t \in [0, t^*] : T(s), I(s), V(s) > 0 \text{ for all } s \in [0, t]\}.$$

Then on the interval $[0, T^*]$ we can make estimations stemming from Gronwall's inequality.

Recall that all constants in the equations are positive. Using Gronwall's inequality, we can place lower bounds on $\frac{dI}{dt}$ and $\frac{dV}{dt}$.

$$\frac{dI}{dt} = kTV - \delta I \geq -\delta I$$

and

$$\frac{dV}{dt} = pI - cV \geq -cV$$

Using an integrating factor, we rewrite these differential inequalities to find

$$I(t) \geq e^{-\delta t} > 0$$

for $t \in [0, T_*]$ and

$$V(t) \geq e^{-ct} > 0$$

for $t \in [0, T^*]$. Similarly, we can place an upper bound on $\frac{dT}{dt}$:

$$\frac{dT}{dt} = \lambda - \mu T - kTV \leq \lambda.$$

Solving for T yields:

$$T(t) \leq T(0) + \lambda t \leq c_1(1 + t).$$

Define the constant c_1 such that $c_1 \geq \max(\lambda, T(0))$. We can sum the equations for $\frac{dI}{dt}$ and $\frac{dV}{dt}$ and place bounds on this sum so that

$$\frac{d}{dt}(I + V) = kTV - \delta I + cV - pI \leq kTV + pI.$$

Recall that we have a bound on T, so we can substitute:

$$\frac{d}{dt}(I + V) \leq kc_1(1 + t)V + pI \leq c_2(1 + t)(I + V)$$

where $c_2 \geq \max(kc_1, p)$. Solving the differential equation yields

$$(I + V)(t) \leq (I(0) + V(0) + c_2)e^{t^2} \leq c_3 e^{t^2}$$

for $t \in [0, T^*]$ where $c_3 \geq 3\max((I(0), V(0), c_2)$. Since $I(t)$ is positive, we can place an upper bound on V:

$$c_3 e^{t^2} \geq (I + V)(t) \geq V(t)$$

We also know that since $V(t)$ is positive, so is $I(t)$.

$$c_3 e^{t^2} \geq (I + V)(t) \geq I(t)$$

With these bounds in place, we can now examine $T(t)$:

$$\begin{aligned} \frac{dT}{dt} &= \lambda - \mu T - kTV \geq -\mu T - kTV \geq -\mu T - kc_3 e^{t^2} T \\ &\geq -c_4(1 + e^{t^2})T \end{aligned}$$

for $t \in [0, T^*]$, where $c_4 \geq \max(\mu, kc_3)$. Shifting that last term to the other side of the equation yields

$$\frac{dT}{dt} + c_4(1 + e^{t^2})T \geq 0$$

Since we know

$$\frac{d}{dt}(T(t) + e^{c_4 \int_0^t (1+e^{\tau^2} d\tau)}) \geq 0,$$

then we find

$$T(t) \geq T(0)e^{-c_4 \int_0^t (1+e^{\tau^2} d\tau)} > 0 \tag{7}$$

for $t \in [0, T^*]$.

Thus, the values of T, I, and V stay strictly positive for all of $[0, T^*]$, including the time T^*. By continuity, there must exist a $t > T^*$ such that $T(t)$, $I(t)$, and $V(t)$ are still positive. This leads to a contradiction, and shows that T, I, and V are strictly positive on the entire interval $[0, T^*]$. Additionally, on this same interval, all of the functions remain bounded, so the interval of existence can be extended further. In fact, the bounds on T, I, and V derived above hold on any compact time interval. Thus, we may extend the time interval on which the solution exists to $[0, t_0]$ for any $t_0 > 0$ and from the above argument, the solutions remain both bounded and positive on $[0, t_0]$. □

With this knowledge, we remain secure in the soundness of our model and know with certainty from a mathematical perspective that it retains biological validity. This also shows that once infected, it is entirely possible that the virus may continue to exist beneath a detectable threshold without doing any damage.

2.3. Stability and Equilibrium of the Deterministic Three Component Model

2.3.1. Equilibria of the System. In order to fully understand the three component model, it is necessary to first study the equilibrium points.

Definition 2.3.1. *Consider the differential equation $y'(t) = f(y(t), t)$. A point is an* equilibrium point *if $y'(t) = f(y(t), t) = 0$ for all $t \in \mathbb{R}$.*

In our case, an equilibrium point is a set of three values corresponding to (T, I, V) with the property that if the system begins at these values, it will remain there indefinitely. In other words, the populations are unchanging from those values, so the rate of change for each population is zero. Knowing that $\frac{d}{dt}$ is zero is what allows us to solve for the precise values. In the case of the Three Component Model, there exist exactly two equilibrium points. We discover them by setting $\frac{dT}{dt}, \frac{dI}{dt}$, and $\frac{dV}{dt}$ equal to zero and solving the resulting equations for T, I, and V. From a biological perspective, we can categorize these points to be when the HIV virus is either extinct from the body, i.e., $I = V = 0$, or when the virus persists within the body $(I \neq 0, V \neq 0)$ as t grows large.

2.3.2. Determining Equilibrium Values. The first such equilibrium exists when $I = 0$ and $V = 0$. This results in a simplification of the above system of equations to:

$$0 = \lambda - \mu T, \tag{8}$$

which in turn shows that the ordered triplet $(T, I, V) = (\frac{\lambda}{\mu}, 0, 0)$ is an equilibrium solution. This particular equilibrium point is also known as viral extinction, since there are no virus particles or infected cells. We will refer to this point as P_1.

To find the second equilibrium, we assume $I \neq 0$ and $V \neq 0$. After setting $\frac{dT}{dt} = \frac{dI}{dt} = \frac{dV}{dt} = 0$, solving for I in the second equation reveals that $I = \frac{kTV}{\delta}$ while solving for I in the third equation gives $I = \frac{cV}{p}$, It follows that since $V \neq 0$, $T = \frac{c\delta}{pk}$. Substituting this value of T into the first equation yields $V = \frac{p\lambda}{c\delta} - \frac{\mu}{k}$ and further substitution shows $I = \frac{\lambda}{\delta} - \frac{\mu c}{kp}$. Thus, there is a second equilibrium at $(T, I, V) = (\frac{c\delta}{pk}, \frac{\lambda}{\delta} - \frac{\mu c}{kp}, \frac{p\lambda}{c\delta} - \frac{\mu}{k})$. Since there are distinct presences of virus particles and infected T-cells, we refer to this point as viral persistence and abbreviate the point as P_2. In terms of biology, we can say P_1 is the case in which an infection exists for a short period of time, then is removed from the body by natural means. The virus does not persist. The

second case, where the system of equations tends to P_2, denotes that situation where the body is unable to clear the infection by itself. If this ends up being the case, than after a certain period of time, the Three Component Model loses its applicability as the infection takes a deeper hold on the body. More complex models, which consider latent infection, effects of macrophages, or cytotoxic immune response, are then required to describe the spread of HIV within the body and its development towards AIDS.

If the system takes on the values of P_1 or P_2 at any time, it will remain at those points indefinitely. Unless the initial conditions for the system are set at an equilibrium, in general, the system may not actually obtain these values. Instead, the system will likely approach them asymptotically, tend to infinity, or cycle between certain values. In the case of the Three Component Model, we will see that the system approaches each equilibrium asymptotically. This is a concept known as asymptotic stability:

DEFINITION 2.3.2. *An equilibrium solution y^* to an ordinary differential equation*

$$y'(t) = f(y(t), t)$$

is said to be (locally) ***asymptotically stable*** *if*

$$\lim_{t\to\infty} |y(t) - y^*| = 0$$

whenever the initial values y_0 are sufficiently close to y^*.

For linear ODEs, it is well-known that the stability properties depend only upon the eigenvalues of the system. However, our model (3CM) is nonlinear, and thus we must rely on linearization and a theorem of Hartman & Grobman [**7**] to unify the behavior of the linear and nonlinear systems.

2.3.3. Linearization and the Jacobian of the System. Linearization is a key concept when examining the equilibrium stability of a system of differential equations. In this case, we approximate the system of differential equations with a linear system at the points P_1 and P_2. This stability analysis perturbs the system from equilibrium and examines if the system returns to the original equilibrium. In order to linearize the system we need to first compute the Jacobian matrix for the system. If a system, S, consists of n functions of m variables, i.e., $F_1(x_1, ..., x_m), ..., F_n(x_1, ...x_m)$ then the Jacobian matrix, J_S, is a matrix of the partial derivative of each function with respect to each variable:

$$J_S = \begin{bmatrix} \frac{\partial F_1}{\partial x_1} & \cdots & \frac{\partial F_1}{\partial x_m} \\ \vdots & \ddots & \vdots \\ \frac{\partial F_n}{\partial x_1} & \cdots & \frac{\partial F_n}{\partial x_m} \end{bmatrix}$$

The matrix J_S provides a linear approximation of a system at any given point, and when evaluated at an equilibrium point P, $J_S(P)$ also encodes information above the nonlinear system.

It is necessary to evaluate a Jacobian matrix at both P_1 and P_2 and examine its corresponding eigenvalues, since analysis of the eigenvalues of the Jacobian matrix evaluated at a equilibrium gives insight into the stability properties of that equilibrium. Specifically, if the eigenvalues of the Jacobian matrix at a point have negative real parts, then that point is classified as an attractor, meaning small perturbations from the equilibrium result in the system returning to that point over time. On the other hand, if one or more of the eigenvalues have positive real part, then small perturbations from equilibrium result in magnifications of those disturbances, and the system shifting away from the point. This point would then be known as a "repeller." For a more detailed look at eigenvalues and their effects on systems of differential equations, see [**10**].

In the case of (3CM), the Jacobian matrix is given by

$$J_{3CM} = \begin{bmatrix} -kV - \mu & 0 & -kT \\ kV & -\delta & kT \\ 0 & p & -c \end{bmatrix}$$

It is possible to determine the signs of the eigenvalues of the Jacobian using a theorem of Routh and Hurwitz [**8**, **14**].

2.3.4. Routh-Hurwitz Theorem.

THEOREM 2.3.3 (Routh-Hurwitz Criteria for a Characteristic Polynomial). *Given the polynomial* $P(x) = x^n + a_1x^{n-1} + \cdots + a_{n-1}x + a_n$ *where each* a_i *is a constant real coefficient, define the* n *Hurwitz matrices using the coefficients* a_i*:*

$$H_1 = \begin{bmatrix} a_1 \end{bmatrix}, H_2 = \begin{bmatrix} a_1 & 1 \\ a_3 & a_2 \end{bmatrix}, H_3 = \begin{bmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{bmatrix}, ...,$$

$$H_n = \begin{bmatrix} a_1 & 1 & 0 & 0 & \dots & 0 \\ a_3 & a_2 & a_1 & 1 & \dots & 0 \\ a_5 & a_4 & a_3 & a_2 & \dots & 0 \\ a_7 & a_6 & a_5 & a_4 & \dots & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & 0 & \dots & a_n \end{bmatrix}$$

All of the roots of $P(x)$ *have negative real part if and only if the determinants of all of the Hurwitz matrices are positive.*

If we consider the case $n = 3$, this theorem simplifies significantly: Given the polynomial $x^3 + a_1x^2 + a_2x + a_3$, the three Hurwitz matrices are as follows:

$$H_1 = \begin{bmatrix} a_1 \end{bmatrix}, H_2 = \begin{bmatrix} a_1 & 1 \\ a_3 & a_2 \end{bmatrix}, H_3 = \begin{bmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ 0 & 0 & a_3 \end{bmatrix}$$

If the determinants of H_1, H_2, and H_3 are all positive, then the roots of the characteristic equation, i.e., the eigenvalues, are all negative or have negative real parts. We can, in fact, make further simplifications.

COROLLARY 2.3.4. *Based on the Routh-Hurwitz criteria, if* $a_1 > 0, a_1a_2 > a_3$, *and* $a_3 > 0$ *then all of the eigenvalues have negative real part, implying that this particular equilibrium is asymptotically stable.*

PROOF. Since $\mathrm{Det}(H_1) = a_1$, $\mathrm{Det}(H_2) = a_1a_2 - a_3$, and $\mathrm{Det}(H_3) = a_1a_2a_3 - {a_3}^2$, it is equivalent to the Routh-Hurwitz criteria to say that:

(1) $a_1 > 0$, so that $\mathrm{Det}(H_1)$ is positive
(2) $a_1a_2 > a_3$, so that $\mathrm{Det}(H_2)$ is positive, and
(3) $a_3 > 0$, so that $\mathrm{Det}(H_3)$is positive.

This last statement follows from the first two. Since $a_1a_2 > a_3$, and $\mathrm{Det}(H_3) = a_1a_2a_3 - a_3^2 = a_3(a_1a_2 - a_3)$, we see that $a_3(a_1a_2 - a_3)$ is positive if and only if $a_3 > 0$.

□

As we will see below, the signs of the roots of this polynomial depend only on a single number known as the reproductive constant, R. Therefore, it is sufficient to examine $R = \frac{kp\lambda}{c\delta\mu}$ and the effect it has on the coefficients of the characteristic equation to determine how R influences stability of equilibrium. This means that in a deterministic model, we can simply examine the value of this coefficient to determine viral persistence or extinction. This is a remarkable result, and estimates of the persistence of HIV upon initial infection have been made solely by Monte-Carlo simulations generating different R-values [**17**].

2.3.5. The Relation between R and Equilibrium Stability. Here, we state two theorems that demonstrate the relationship between the R-value and which equilibrium is asymptotically stable.

THEOREM 2.3.5. P_1 *is an asymptotically stable equilibrium if and only if* R *is less than 1.*

PROOF. Evaluating the Jacobian at $P_1 = (\frac{\lambda}{\mu}, 0, 0)$ results in

$$J_{3CM}(P_1) = \begin{bmatrix} -\mu & 0 & -\frac{k\lambda}{\mu} \\ 0 & -\delta & \frac{k\lambda}{\mu} \\ 0 & p & -c \end{bmatrix}$$

The characteristic equation of $J_{3CM}(P1)$ is:

$$(-\mu - x)\left((-\delta - x)(-c - x) - \frac{kp\lambda}{\mu}\right) = 0$$

which expands to:

$$x^3 + a_1x^2 + a_2x + a_3 = 0$$

where

$$a_1 = c + \delta + \mu a_2 = c\delta + c\mu + \delta\mu - \frac{kp\lambda}{\mu} a_3 = c\delta\mu - kp\lambda.$$

If the eigenvalues have negative real part, then the Routh-Hurwitz criteria are satisfied, which implies that $a_3 > 0$. This means $c\delta\mu - kp\lambda > 0$ and it follows that $c\delta\mu > kp\lambda$ leading to $1 > \frac{kp\lambda}{c\delta\mu} = R$. Simply put, an asymptotically stable equilibrium at P_1 implies that $R < 1$.

Conversely, if $R < 1$, then $a_3 > 0$, and since all the coefficients are positive, it is clear that $a_1 > 0$. Additionally, since $c\delta\mu > kp\lambda$, then $c\delta > \frac{kp\lambda}{\mu}$ and $a_2 = c\delta + c\mu + \delta\mu - \frac{kp\lambda}{\mu} > c\delta + c\mu + \delta\mu - c\delta = c\mu + c\delta$. So,

$$a_1a_2 = (c + \delta + \mu)\left(c\delta + c\mu + \delta\mu - \frac{kp\lambda}{\mu}\right) > (c + \delta + \mu)(c\mu + \delta\mu) > c\delta\mu > c\delta\mu - kp\lambda = a_3$$

that is, $R < 1$ implies P_1 is an asymptotically stable equilibrium for (3CM). □

Thus, "$R < 1$" and "P_1 is an asymptotically stable attracting equilibrium" are equivalent statements

THEOREM 2.3.6. *P_2 is an asymptotically stable equilibrium if and only if R is greater than one.*

PROOF. The analysis for $P_2 = (\frac{c\delta}{pk}, \frac{\lambda}{\delta} - \frac{\mu c}{kp}, \frac{p\lambda}{c\delta} - \frac{\mu}{k})$ is similar to that of P_1. The analysis begins by linearizing the system (3CM) about P_2 and examining the characteristic equation. The Jacobian is slightly more complicated in this case:

$$J_{3CM}(P_2) = \begin{bmatrix} -k(\frac{p\lambda}{c\delta} - \frac{\mu}{k}) - \mu & 0 & -k(\frac{c\delta}{pk}) \\ k(\frac{p\lambda}{c\delta} - \frac{\mu}{k}) & -\delta & k(\frac{c\delta}{pk}) \\ 0 & p & -c \end{bmatrix}$$

$$= \begin{bmatrix} -(\frac{k\lambda p}{c\delta}) & 0 & -(\frac{c\delta}{p}) \\ \frac{k\lambda p}{c\delta} - \mu & -\delta & \frac{c\delta}{p} \\ 0 & p & -c \end{bmatrix}$$

and results in the characteristic equation

$$\left(\frac{-k\lambda p}{c\delta} - x\right)\Big((-\delta - x)(-c - x) - c\delta)\Big) + \frac{-c\delta}{p}\left(\frac{k\lambda p}{c\delta} - \mu\right)p = 0$$

with expanded form

$$x^3 + a_1x^2 + a_2x + a_3 = 0$$

where

$$a_1 = c + \delta + \frac{k\lambda p}{c\delta} a_2 = \frac{k\lambda p}{\delta} + \frac{k\lambda p}{c} a_3 = k\lambda p - c\delta\mu.$$

Since the Routh-Hurwitz criteria apply in this case as well, it is sufficient to show that $R > 1$ implies $a_1 > 0, a_1a_2 > a_3$, and $a_3 > 0$ and vice versa.

It is clear that if the Routh-Hurwitz criteria are satisfied then $R > 1$, since $a_3 = k\lambda p - c\delta\mu > 0 \Leftrightarrow k\lambda p > c\delta\mu \Leftrightarrow \frac{k\lambda p}{c\delta\mu} = R > 1$. Additionally, since all the coefficients in the system are positive, a_1 will be positive as well. Finally,

$$a_1 a_2 = \left(c + \delta + \frac{k\lambda p}{c\delta}\right)\left(\frac{k\lambda p}{\delta} + \frac{k\lambda p}{c}\right) > kp\lambda > kp\lambda - c\delta\mu = a_3.$$

□

Thus, $R > 1$ implies that P_2 is an asymptotically stable equilibrium, and in fact, is both a necessary and sufficient condition. This analysis reveals one very important fact about the overall system: the long term behavior of the system depends only on the value of R. If R is greater than one, then the system tends towards an end state with a non-zero population of infected cells and virions (**persistence**), but if R is less than one, then the final equilibrium is a state with no virus or infection (**extinction**). Finally, we remark that in the rare event that $R = 1$, the equilibria P_1 and P_2 are identical. From the analysis above, then, it follows that this joint equilibrium is also locally asymptotically stable.

The figure (2.1) serves as an example that illustrates what the equilibriums looks like when R changes. The top graph shows what happens when R is less than one, while the lower graph shows what happens when R is greater than one. While the coefficients are not biologically relevant, the figure remains mathematically accurate.

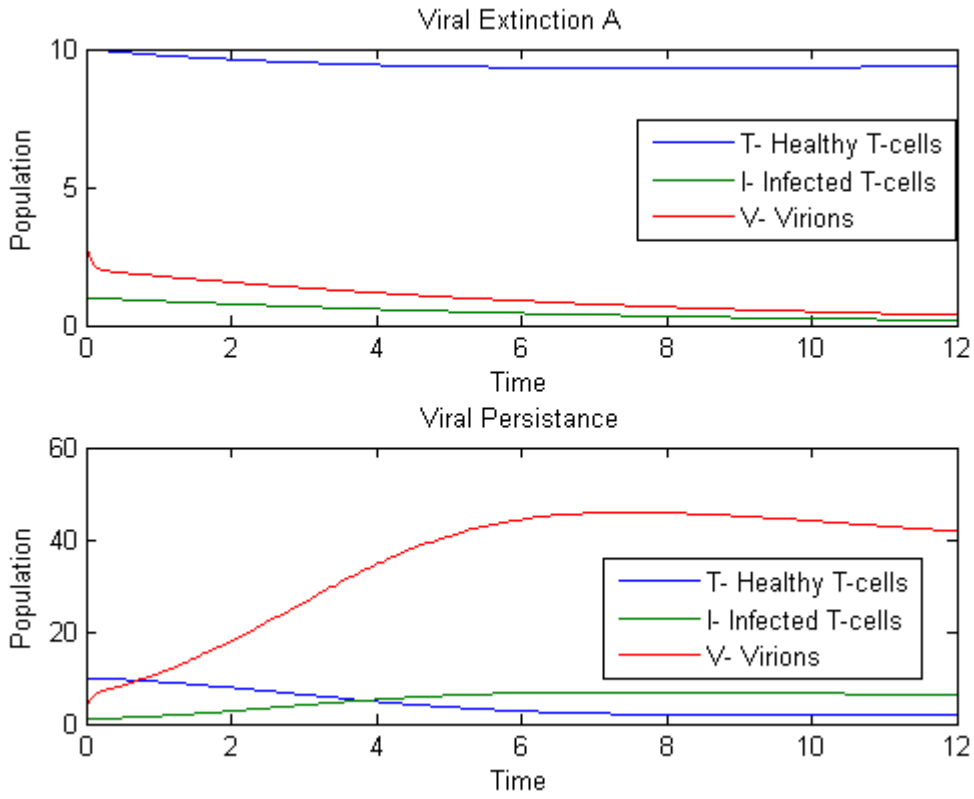


FIGURE 2.1. Graphs of the 3CM with illustrative coefficients for $R < 1$(top) and $R > 1$(bottom).

2.4. Numerical Results

The simulation of the Three Component Model was developed in MATLAB, and there were several different paths taken to get final probability distributions, and each of them differ in their method of computation.

2.4.1. General Method of Coding. All of the code used to simulate the Three Component Model shares the same basic characteristics. In each individual trial, initial conditions and coefficients are chosen, the R-value is calculated, then the system of equations is simulated. This is done deterministically, discretely, or stochastically. The end states of each simulation are recorded and compared with the viral detection threshold, and in some cases, we determine to what degree, if any, correlation exists between the end state, the R-value, and the initial conditions. We also examine what the average sample path and average end states look like.

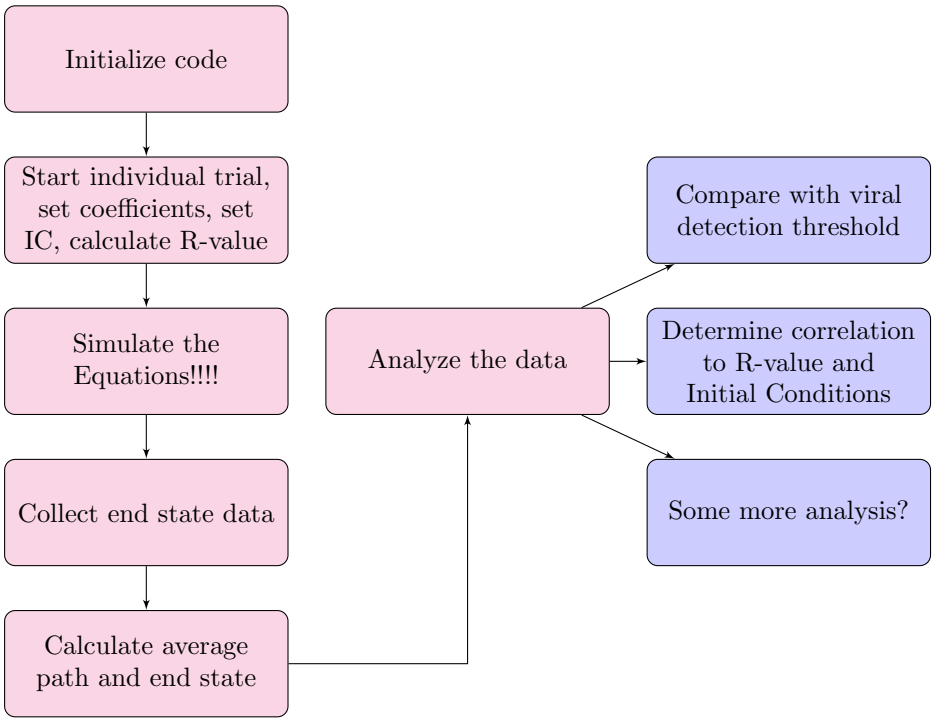


FIGURE 2.2. A flow chart representation of the functions involved in coding

2.4.2. Common Features of Simulations. There are several functions used in MATLAB that are common to nearly every simulation. They all stem from a specially designed random number generator. This function permits the generation of normal distributions that are truncated on one or both ends. Known as `truncatednormal.m` throughout the project, we use this function to create positive or non-negative coefficients and initial conditions that are both statistically representative and biologically meaningful. There are child functions of this random number generator that create truncated normally distributed starting conditions and coefficients.

In addition to functions used throughout all the simulations, several numerical values remain the same regardless of the method of simulation used. For instance, there exists a lowest possible amount of virus detectable by medical technology. 40-75 virus particles per micro-liter of blood is the range of values given by scientific literature We use this lower value, 40 $\frac{particles}{\mu L}$ as our threshold. We also run each simulation

from initial infection to sixty days beyond that point. At that point, the populations are stable, and a determination of viral extinction can be made.

Coding the three component model deterministically, while not fully representative of the randomness inherent in real life, still offers two distinct advantages. First, this type of simulation is straightforward from a computational perspective, and second, this simulation allows us to isolate the effects of coefficients and initial conditions to a much greater degree than permissible in the stochastic simulations. Since we recall that the equations for the deterministic model and for the expected value of the stochastic model are the same, we can imagine this simulation as looking at the average of an infinite number of stochastic simulations.

2.4.3. The Basic Deterministic Model. The Deterministic Model, when simulated in its most basic sense, is simulated over one set of coefficients and initial conditions. The system of differential equations, along with the initial values and time interval over which it is to be simulated are given to the MATLAB function `ode45.m`, which uses a fifth order Runge-Kutta method to generate the sample path for each population. With one trial, it is a simple matter to compare the end virus population to the detection threshold and determine persistence or extinction from that.

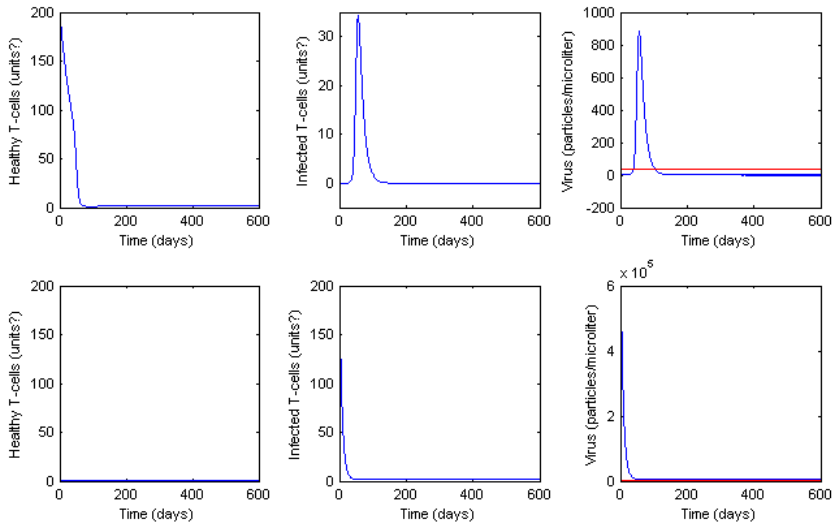


FIGURE 2.3. Two simulations of the deterministic 3CM with mean standard ICs

Figure 2.3 shows what one run of the deterministic code looks like. The red line represents the detectable virus threshold. Note that this demonstrates the two possible end states for the system. We can either have viral persistence, as demonstrated by the lower set of figures, or we can have viral extinction, as demonstrated by the upper set of figures. These figures used the values of the coefficients that would maximize and minimize R, in order that a clear distinction could be made about how these coefficients affect the end results.

2.4.4. Deterministic Model with Random Valued Coefficients. The next step in modeling the deterministic system is to randomize the coefficients used in the equations. We recall that these coefficients vary from person to person, and are representative of various biological traits. Because of this, certain restrictions and conditions are placed upon them. First, we know that in order to be biologically meaningful, we must have these values be positive. It would make no sense, for instance, for the T-cell growth rate to be inherently negative. Second, we assume these values to be normally distributed. Therefore, when we draw upon these coefficients, we take the mean and standard deviation given by existing data, and use a function in MATLAB designed to draw a random value from a truncated normal distribution.

For each of 10000 trials, we generate a set of coefficients from these truncated normal distributions. With these values, the standard initial conditions, and the standard time interval, we use the built in MATLAB function `ode45.m` again to computationally solve the deterministic system. We record the sample paths for each run, and those with R-values greater than one are colored in cyan (or light blue), while those sample paths whose equations have R-values less than one are colored magenta (or purple).

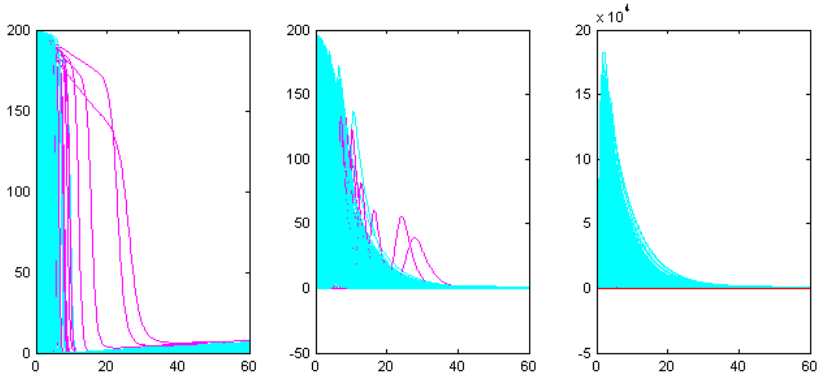


FIGURE 2.4. 1000 simulations of the deterministic model with different coefficients. Standard IC

In the end, the code gives an array of data consisting ofthe end population values and the R-value for each trial . We place the data into histograms to give a better idea of how many end states reach which value. Again, when we look at the viral end states, the red line represents the detection threshold. In this particular example, we see that we have over 2000 cases (2140 to be exact) in which the virus population is undetectable after sixty days.

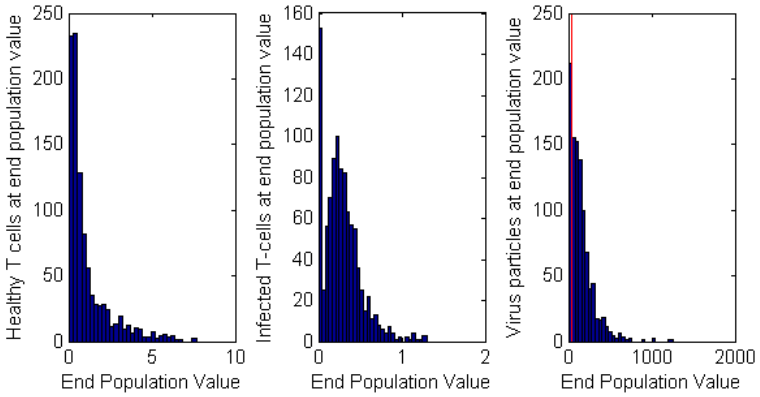


FIGURE 2.5. 1000 simulations of the deterministic model with different coefficients. Standard IC

Of the coefficient sets generated, 211 had corresponding R-values less than one. This is similar to the results of Tuckwell and Shipman [**17**], whose estimation for R-values of less than one ranged around 2%. For all of these sets, the end virus population was beneath the detectable threshold.

CHAPTER 3

Stochastic Differential Equations and Ito's Lemma

3.1. The Birth Death Model

While knowledge of the deterministic Three Component Model is useful, our goal is to extend this to a stochastic model. In order to construct the stochastic three component model, we first create a stochastic model of a simpler system. This will serve to illustrate some ideas and demonstrate that they are special cases of general theorems we use later to create a stochastic model of the Three Component Model.

A stochastic system better represents the randomness inherent in everyday life. When used with one set of coefficients, the deterministic model tells us what happens to one patient one time after an initial infection. On the other hand, with a stochastic model, we see the *probability distribution* of this one person's viral state. This is a much more valuable piece of information, because from it, we can see not only which end states are more likely, but how likely they are.

Let's begin by considering the ordinary differential equation:

$$\begin{aligned} &\frac{dX}{dt} = bX - dX \\ &X(0) = x_0 \end{aligned} \tag{9}$$

where $b, d > 0$ and $x_0 \geq 0$. This is known as the birth-death model.

3.1.1. A random walk related to the birth-death model. We wish to create a random walk that behaves in such a way that the expected value of the random walk at time t is related to the differential equation (9). To do this, we first define a discrete time random walk $X(t)$ that starts at a given point x_0 and assume that over a given time interval, Δt, the value of $X(t)$ can increase by some amount, Δx , decrease by Δx, or remain the same. If we start at a given time t and population x, the next time step is given by:

$$X(t + \Delta t) \in \{X(t) + \Delta x, X(t) - \Delta x, X(t)\} \tag{10}$$

We refer to these population changes, either positive or negative, as spatial changes, and each of these possibilities of spatial change has a probability associated with it. Define $P_+(t)$ to be the probability of a positive spatial change over a time step Δt starting from time t, define $P_-(t)$ to be the probability of a negative spatial change over a time step Δt starting at time t, and define $P_0(t)$ to be the probability of no change over a time step Δt starting at time t. In other words, if we let $\mathbb{P}(e)$ denote the probability of the event e then

$$\begin{aligned} P_+(t) &= \mathbb{P}(X(t + \Delta t) = X(t) + \Delta x) \\ P_-(t) &= \mathbb{P}(X(t + \Delta t) = X(t) - \Delta x) \\ P_0(t) &= \mathbb{P}(X(t + \Delta t) = X(t)) \end{aligned} \tag{11}$$

The values of the probabilities are chosen such that they match the differential equation of the birth death model, and are given by $P_+(t) = bX(t)\Delta t$, $P_-(t) = dX(t)\Delta t$, and $P_0(t) = 1 - (P_+(t) + P_-(t))$. Note that we cannot a priori guarantee that P_+, P_- and P_0 are a probability distribution. However, we proceed with a formal calculation. Let us assume that it is possible to choose Δt, in such a way that $P_+ + P_-$ is less than one, and as such, $P_+(t) + P_-(t) + P_0(t) = 1$. These values were chosen so that the expected value of each step satisfies $\mathbb{E}[X(t + \Delta t) - X(t)] = (b - d)\Delta x$. We will see this later on.

Since this model is discrete and the value of X at each time step only depends on the value at the previous step, we know that if $X(t+\Delta t)=x$, there are only three possibilities that can lead to this state, namely:

(1) The value of $X(t)$ increased so that

$$X(t)=x-\Delta x \text{ and } X(t+\Delta t)=x$$

(2) The value of $X(t)$ decreased so that

$$X(t)=x+\Delta x \text{ and } X(t+\Delta t)=x$$

(3) The value of $X(t)$ remained the same so that

$$X(t)=x \text{ and } X(t+\Delta t)=x.$$

It is important to note that these events are disjoint, and $X(t+\Delta t)=x$ is the union of these events. Therefore, the probability of the event $X(t+\Delta t)=x$ is equal to the sum of the probabilities of the these three events. We have:

$$\begin{aligned}\mathbb{P}(X(t+\Delta t)=x)= &\ \mathbb{P}(X(t+\Delta t)=x\cap X(t)=x-\Delta x)\\ &+\mathbb{P}(X(t+\Delta t)=x\cap X(t)=x+\Delta x)\\ &+\mathbb{P}(X(t+\Delta t)=x\cap X(t)=x)\end{aligned} \tag{12}$$

Since $\mathbb{P}(A|B)=\frac{\mathbb{P}(A\cap B)}{\mathbb{P}(B)}$, it follows that $\mathbb{P}(A\cap B)=\mathbb{P}(A|B)\mathbb{P}(B)$, and because of this,

$$\begin{aligned}&\mathbb{P}(X(t+\Delta t)=x\cap X(t)=x-\Delta x)=\\ &\mathbb{P}(X(t+\Delta t)=x|X(t)=x-\Delta x)\mathbb{P}(X(t)=x-\Delta x)\end{aligned} \tag{13}$$

From above, we know that $\mathbb{P}(X(t+\Delta t)=x|X(t)=x-\Delta x)$ is the same as $P_+(t)$, and similarly for $P_-(t)$ and $P_0(t)$. The above equations then reduce to:

$$\begin{aligned}\mathbb{P}(X(t+\Delta t)=x)= &\ \mathbb{P}(X(t)=x-\Delta x)(P_+(t))\\ &+\mathbb{P}(X(t)=x+\Delta x)(P_-(t))\\ &+\mathbb{P}(X(t)=x)(P_0(t))\end{aligned} \tag{14}$$

Recall the definition of expected value:

Definition 3.1.1. *Consider a random variable X that has possible outcomes $x_1,\dots,x_n$ with corresponding probabilities $p_1,\dots,p_n$. The* expected value *of X is given by $\mathbb{E}[X]=\sum_{i=1}^n p_i x_i$.*

Define $Y(t):=X(t+\Delta t)-X(t)$. We have,

$$\begin{aligned}\mathbb{E}[Y(t)|X(t)=x] &= (x+\Delta x-x)bx\Delta t+(x-\Delta x-x)dx\Delta t\\ &\quad +(x-x)(1-bx\Delta t-dx\Delta t)\\ &= \Delta x bx\Delta t-\Delta x dx\Delta t+0(1-bx(\Delta t)-dx(\Delta t))\\ &= \Delta x bx\Delta t-\Delta x dx\Delta t\\ &= (b-d)x\Delta x\Delta t\end{aligned}$$

Now consider the infinitesimal mean

$$\lim_{\Delta t\to 0}\frac{\mathbb{E}[Y(t)|X(t)=x]}{\Delta t} = (b-d)x\Delta x$$

We can do the same computations with the second moment, where $Y(t)$ is defined as above:

$$\begin{aligned}\mathbb{E}[Y(t)^2|X(t)=x] &= (x+\Delta x-x)^2 bX(t)\Delta t + (x-\Delta x-x)^2 dx\Delta t \\ &\quad + (x-x)^2(1-bx\Delta t - dx)(\Delta t) \\ &= (\Delta x)^2 bx\Delta t + (\Delta x)^2 dx(\Delta t) + 0(1-bx\Delta t - dx\Delta t) \\ &= (b+d)x(\Delta x)^2\Delta t \\ \frac{\mathbb{E}[Y(t)^2|X(t)=x]}{\Delta t} &= (b+d)x(\Delta x)^2\end{aligned}$$

Then consider the infinitesimal second moment:

$$\lim_{\Delta t\to 0}\frac{\mathbb{E}[Y(t)^2|X(t)=x]}{\Delta t} = (b+d)x(\Delta x)^2$$

3.1.2. A Partial Differential Equation associated with the Random Walk. Define $v(x,t)$ to be $\mathbb{P}(X(t)=x|X(0)=x_0)$. We find

$$v(x,t+\Delta t) = v(x-\Delta x,t)P_+(t) + v(x+\Delta x,t)P_-(t) + v(x,t)P_0(t)$$

Replacing with the values for $P_+(t)$, $P_-(t)$, and $P_0(t)$ yields:

$$\begin{aligned}v(x,t+\Delta t) = v(x-\Delta x,t)bX(t)\Delta t + v(x+\Delta x,t)dX(t)\Delta t \\ +v(x,t)(1-(b+d)X(t)\Delta t)\end{aligned}$$

Subtract $v(x,t)$ from both sides, divide by Δt, and recall that at time t, $X(t)=x$:

$$\begin{aligned}\frac{v(x,t+\Delta t)-v(x,t)}{\Delta t} = v(x-\Delta x,t)bx + v(x+\Delta x,t)dx \\ +v(x,t)(b+d)(x)\end{aligned} \tag{15}$$

Define a new function, w given by $w(x,t)=xv(x,t)$ and rewrite (15):

$$\begin{aligned}\frac{v(x,t+\Delta t)-v(x,t)}{\Delta t} &= bw(x-\Delta x,t) + dw(x+\Delta x,t) + (b+d)w(x,t) \\ &= b(w(x-\Delta x,t)-w(x,t)) \\ &\quad + d(w(x+\Delta x,t)-w(x,t))\end{aligned}$$

From Taylor's Theorem, we know in that general for any continuous function with continuous derivatives, denoted f, we have

$$f(x-\Delta x) = f(x) - \Delta x f_x(x) + \frac{(\Delta x)^2}{2}f_{xx}(x) + O((\Delta x)^3) \tag{16}$$

The term $O((\Delta x)^3)$ indicates that the expansion continues, but the value of the remainder depends on $(\Delta x)^3$ and is close to 0 when Δx is small, as it is in this case. So we can expand as above to find,

$$w(x\pm\Delta x) - w(x,t) = \pm(\Delta x)w_x(x,t) + \frac{(\Delta x)^2}{2}w_{xx}(x,t) + O((\Delta x)^3).$$

The right hand side of (16) then becomes

$$b((-\Delta x)w_x(x,t) + \frac{(\Delta x)^2}{2}w_{xx}(x,t)) + (d)((\Delta x)w_x(x,t) + \frac{(\Delta x)^2}{2}w_{xx}(x,t)) + O((\Delta x)^3)$$

which reduces to $(d-b)(\Delta x)w_x(x,t) + (b+d)(\frac{(\Delta x)^2}{2}w_{xx}(x,t))$. From this position, we are left with:

$$\frac{v(x,t+\Delta t)-v(x,t)}{\Delta t} = (d-b)(\Delta x)w_x(x,t) + (b+d)\left(\frac{(\Delta x)^2}{2}w_{xx}(x,t)\right) + O((\Delta x)^3). \tag{17}$$

We note that this equation looks very similar to a discretized version of the partial differential equation

$$\frac{\partial v}{\partial t} = -\frac{\partial}{\partial x}\Big((d-b)xv(x,t)\Big) + \frac{1}{2}\frac{\partial^2}{\partial x^2}\Big((b+d)xv(x,t)\Big) \tag{18}$$

In fact, taking the limit as Δt and Δx tend to zero in a specific way, one can recover this equation exactly. Additional details can be found in [**1**].

3.1.3. Transitioning from a PDE to a Stochastic Differential Equation. From [**1**], we get that for small Δt and Δx, the probability distributions in the partial differential equation above are approximately the same as the probability distributions for solutions to the discrete stochastic process. Therefore, the discrete stochastic process that models this ordinary differential equation is:

$$dX(t) = (b-d)X(t)dt + \sqrt{(b+d)X(t)}dW_t \tag{19}$$

Later on in the paper, the terms W_t and dW_t will be defined and explained in more detail, but for now, we can consider them to be the added "randomness" to the system.

From [**16**], we know something similar. If we are given a discrete system, and desire a stochastic differential equation of the form:

$$dX(t) = F(X)dt + G(X)dW_t, \tag{20}$$

then the F term consists of the infinitesimal mean from the discrete system and the G term is the infinitesimal second moment. Therefore, if we desire a stochastic differential equation for the three component model, the best place to start is to discritize the system.

3.2. Brownian Motion

3.2.1. Stochastic Processes. In order to more realistically describe situations seen in real life, some models include stochastic processes. In order to define a stochastic process we begin with the definition of a probability space, then move on to define a random variable, and finally a stochastic process.

Definition 3.2.1 (Probability Space). A *probability space* is a triple (Ω, U, P) consisting of

(1) A *sample space* Ω, which is a set that consists of all possible outcomes.
(2) A *σ-algebra* U. A σ-algebra is a collection of subsets of Ω that contains the empty set $\emptyset$, Ω, and is closed under countable unions and complements.
(3) A *probability measure* $P : U \to [0,1]$ such that if $U_1, U_2, \cdots \in U$ are mutually disjoint, then $P(\cup_{k=1}^{\infty} U_k) = \sum_{k=1}^{\infty} P(U_k)$.

This definition of a probability space allows us to define a random variable:

Definition 3.2.2 (Random Variable). Given a probability space (Ω, U, P), a *random variable* is a function $X : \Omega \to \mathbb{R}$ such that for all $r \in \mathbb{R}$, the set $\{\omega | X(\omega) \leq r\} \in U$

We can view a stochastic process as a random variable indexed by time.

Definition 3.2.3 (Stochastic Process). Given a probability space (Ω, U, P), a *stochastic process* is a function $X : \Omega \times \mathbb{R} \to \mathbb{R}$ such that for each $t \in \mathbb{R}$, $X(t) = X_t$ is a random variable.

3.2.2. Sample Path. With this in mind, we can define a sample path.

Definition 3.2.4 (Sample path). Let $X : \Omega \times \mathbb{R} \to \mathbb{R}$ be a stochastic process. For each $\omega \in \Omega$ the function $t \mapsto X(\omega, t)$ is called a *sample path.*

Since X_t consists of a set of random variables indexed by time, the sample path of X_t for ω would be the collection of values $X_t(\omega)$. This is a function from time to the possible outcomes of X_t. We can now define a continuous stochastic process.

Definition 3.2.5 (Continuous Stochastic Process). A continuous stochastic process is a stochastic process such that for every $\omega \in \Omega$, $X_\omega(t)$ is a continuous function for $t \in [a, b]$.

3.2.3. Brownian Motion. The most basic stochastic process is Brownian motion, which is also known as the Wiener process. Originally used to describe the motion of particles suspended within a fluid, Brownian motion is named after the botanist Robert Brown. In the late nineteenth century, he observed that pollen floating in water appeared to move about in a random manner. When he replaced the pollen with inorganic material, he noticed that the motion persisted. Upon plotting the motion over time, he noticed that it appeared to have no tangent anywhere, and regardless of the magnification or scale, the motion appeared random. This motion was later described by Albert Einstein to be caused by molecular level forces on the particle. These impacts on the aggregate cancel each other out, but at any particular time, it is highly likely that one side of the particle is experiencing more force than the other. This causes the particle to move about. Mathematically, this process was described first by Norbert Wiener, after whom the process is named. We abbreviate the Wiener process $W(t)$ or W_t for each $t \in [0, T]$. This process possesses three important and distinctive properties:

(1) $W(0) = 0$
(2) $W(t)$ is normally distributed with mean 0 and variance t.
(3) For any sequence $0 = t_0 < t_1, < \cdots <, t_n = T$, the random variables $W(t_1) - W(t_0), W(t_2) - W(t_1), \ldots, W(t_n) - W(t_{n-1})$ are independent.

We can consider Brownian motion to be the limit of a symmetric random walk as both the spatial size and time step go to zero, or perhaps consider it to be the integral of noise independent of frequency.

It is important to note that for each t, $W(t)$ is a random variable, with expected value 0. However, if we were to graph several different sample paths of $W(t)$, we would note that they have entirely different graphs.

Figure 3.1 traces out different sample paths for Brownian Motion from time $t = 0$ to $t = 1000$. We note that the spread or variance in each path grows with time. Each solid black line represents one standard deviation away from the mean. If we were to graph more sample paths, and observe at any given time their value, we would see that the distribution of the values at that time closely resembled a normal distribution. This is visible in the histogram drawn from the end values.

3.3. Stochastic Integration

A stochastic differential equation (SDE) is an equation of the form

$$dX(t) = F(X(t), t)dt + G(X(t), t)dW_t,$$

where F, G are functions and W_t is Brownian motion. In order to give proper meaning to the above equation we would need to develop a significant amount of theory that is outside the scope of this project and a typical undergraduate syllabus.

Instead we will settle for a more heuristic approach and provide references. The manuscript of Evans [**4**] is particularly good.

We can gain some insight into the SDE by discretizing it:

Examining the discrete case, we see a stochastic differential equation takes the form

$$X(t + h) = X(t) + hdX = X(t) + F(X(t), t)h + G(X(t), t)(W_{t+h} - W_t) \tag{21}$$

Recall from the definition of Brownian Motion that the term $W_{t+h} - W_t$ is a normally distributed random variable with mean 0 and variance h. A stochastic differential equation is typically given in the form $dX = Fdt + GdW$, where X is the unknown stochastic process, F is a deterministic, or drift function, and G is a random, or diffusion term. Both F and G can be functions of $X(t)$ and t, and exist in the following function spaces:

- $\mathbb{L}^1(0, T)$ is the space of stochastic processes F such that $\mathbb{E}\left[\int_0^T |F|dW\right] < +\infty$
- $\mathbb{L}^2(0, T)$ is the space of stochastic processes G such that $\mathbb{E}\left[\int_0^T G^2 dW\right] < +\infty$

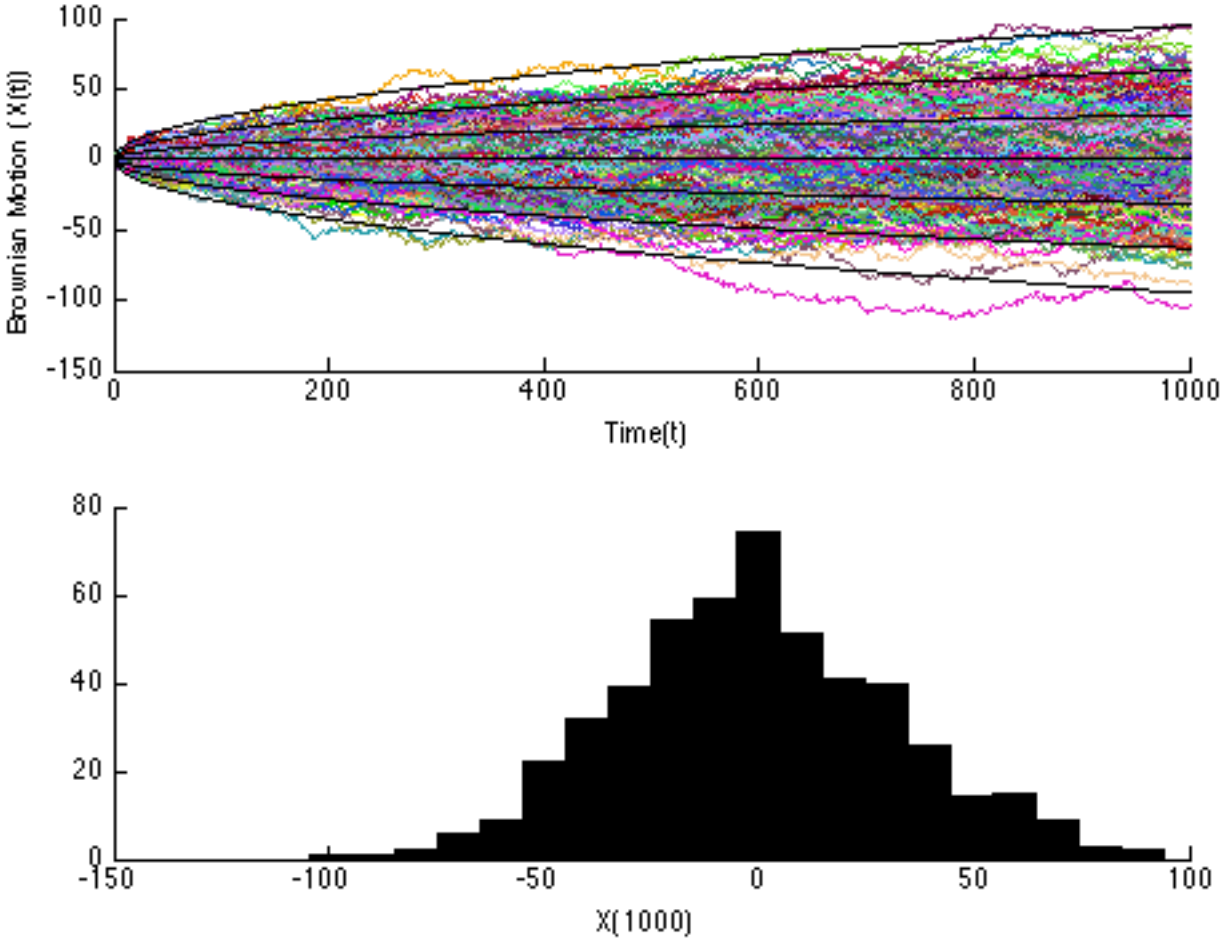


FIGURE 3.1. Several sample paths of Brownian Motion with the curves $x = \sqrt{t}$ and $x = -\sqrt{t}$ outlining the standard deviation (top), and a histogram of the distribution of Brownian Motion increments (bottom).

As noted in [**4**], these spaces must include the additional technical condition that the stochastic processes be progressively measurable. We omit details related to this point and instead refer the reader to [**4**] for further details.

When dealing with stochastic differential equations, we will have a time interval, $[0, T]$, and see terms such as "$dX = Fdt + GdW$", where X, F and G are stochastic processes, with $X, F \in \mathbb{L}^1([0, T])$ and $G \in \mathbb{L}^2([0, T])$. This dX term has no intrinsic meaning, but rather, implies that given two values, s and $r \in [0, T]$,

$$X(s) - X(r) = \int_r^s Fdt + \int_r^s GdW \tag{22}$$

In order to understand what this actually means, we should break the differential down into its component parts. The left side of the equation is simple. It simply subtracts the value of the stochastic process X at

time r from the value of X at s. Remember that both of these evaluations are random variables. The right side of the equation consists of two parts: $\int_r^s F dt$ and $\int_r^s G dW$. We shall examine each of these separately.

Recall in ordinary calculus how integrals were introduced. After choosing a large number of steps n and partitioning the interval $[r, s]$ into $t_0 = r, t_1 = r + \frac{s-r}{n}, t_2 = r + \frac{2(s-r)}{n}, \ldots, t_n = s$, the integral was approximated by Riemann sums so that

$$\int_r^s f dt \approx \sum_{k=0}^{n-1} f(t_k) \frac{s-r}{n}. \tag{23}$$

Something similar can be done for a stochastic process $F(t)$ integrated with respect to time. We discretize the time interval into small parts and evaluate the process at each point of the partition. The resulting integral appears identical to that above

$$\int_r^s F dt \approx \sum_{k=0}^{n-1} F(t_k) \frac{s-r}{n}. \tag{24}$$

but, contrasting with an ordinary integral, however, the result of this integration is now a random variable, not a real number. Similarly for $\int_r^s G dW$, we can approximate the integral as defined by Evans [**4**]:

$$\int_r^s G dW \approx \sum_{k=0}^{n-1} G(t_k)(W_{t_{k+1}} - W_{t_k}). \tag{25}$$

Note that this is also a random variable.

Just as in ordinary calculus not all functions F, G can be integrated as above. Certain technical assumptions must be made about the adaptability of the stochastic process X to the filtration generated by Brownian motion. These ideas are beyond the scope of this project.

3.3.1. Basic properties. There are two fundamental properties of the Ito integral that we need.

The first property tells us that if we have any function in $\mathbb{L}^1([0, T])$ integrated with respect to Brownian Motion, then the expected value of the integral is zero. In other words,

$$\mathbb{E}\left[\left(\int_0^T F dW\right)\right] = 0 \tag{26}$$

The second is the *Ito Isometry*. The Ito Isometry is an important relation between dW and dt, and it permits us to use a heuristic that is vital in our coding methods.

Theorem 3.3.1 (Ito Isometry).

$$\mathbb{E}\left[\left(\int_0^T F dW\right)^2\right] = \mathbb{E}\left[\int_0^T F^2 dt\right] \tag{27}$$

The proof is given in [**4**]. Additionally, an important special case of this theorem arises when $F \equiv 1$, namely

$$\mathbb{E}\left[\left(\int_0^T dW\right)^2\right] = T - 0 = T \tag{28}$$

This leads to the heuristic $dW \approx \sqrt{dt}$ or $dt \approx dW^2$, which will be used for various calculations.

3.3.2. Stochastic Calculus. Based on previous discussion, there are several properties of stochastic differentials worth exploring. The first is that the differentiation operator is linear. So given two stochastic processes, X and Y, then we can compute the differential of any linear combination $d(aX+bY) = a\,dX+b\,dY$ where $a, b \in \mathbb{R}$. This is identical to what we see in ordinary calculus.

Contrastingly, the product rule for stochastic calculus differs from ordinary calculus. Given two stochastic processes, X_1 and X_2, such that $dX_1 = F_1dt + G_1dW$ and $dX_2 = F_2dt + G_2dW$, we find

$$d(X_1X_2) = X_1dX_2 + X_2dX_1 + G_1G_2dt. \tag{29}$$

3.4. Ito's Lemma

With everything above, we can state Ito's Lemma. Ito's Lemma, which is also known as Ito's Formula, is one of the most important results in stochastic calculus because it allows us to find solutions for stochastic differential equations, by providing an analogous version of the Chain Rule. We will use the Ito Isometry to develop a partial differential equation to solve for the probability distribution of the stochastic three component model at any time.

The formal statement of Ito's Formula follows:

THEOREM 3.4.1 (Ito's Lemma). *Suppose that X is a stochastic process with differential*

$$dX = Fdt + GdW \tag{30}$$

with $F \in \mathbb{L}^1([0,T])$ and $G \in \mathbb{L}^2([0,T])$. Assume that a function $u : \mathbb{R} \times [0,T] \to \mathbb{R}$ is continuous with continuous first order partial derivatives and a continuous second order partial derivative $\frac{\partial^2 u}{\partial x^2}$. Define the stochastic process

$$Y(t) := u(X(t), t). \tag{31}$$

The stochastic differential for Y is then

$$\begin{aligned} dY &= \tfrac{\partial u}{\partial t}dt + \tfrac{\partial u}{\partial x}dX + \tfrac{1}{2}\tfrac{\partial^2 u}{\partial x^2}dt \\ &= (\tfrac{\partial u}{\partial t} + \tfrac{\partial u}{\partial x}F + \tfrac{\partial^2 u}{\partial x^2}G^2)dt + \tfrac{\partial u}{\partial x}GdW \end{aligned} \tag{32}$$

The proof for Ito's Lemma is actually remarkably simple, and an outline of the steps involved follows:

(1) By using the stochastic product rule and mathematical induction, prove Ito's Formula for functions of the form $Y(t) := u(X(t), t) = (X(t))^n$.
(2) Use the fact that all functions are limits of polynomials to prove Ito's Formula for functions that are polynomials of $X(t)$ or t, that is a function that is of the form $P(X(t)) = c_n(X(t))^n + c_{n-1}(X(t))^{n-1} + \cdots + c_1(X(t)) + c_o$.
(3) Use the product rule to prove Ito's Formula for separable functions of $X(t)$ and t, that is, for a function $u(X(t), t) = f(X(t))g(t)$.
(4) Use the above facts to show that if any sequence of polynomials, $Y_n = u_n(X(t), t)$ converges to a function $Y = u(X(t), t)$ (with the derivatives $\frac{\partial u_n}{\partial t}$, $\frac{\partial u_n}{\partial x}$, and $\frac{\partial^2 u_n}{\partial x^2}$ likewise converging to $\frac{\partial u}{\partial t}$, $\frac{\partial u}{\partial x}$, and $\frac{\partial^2 u}{\partial x^2}$), then the differentials dY_n converge to dY.

3.4.1. Multi-dimensional Ito's Formula. Extending Ito's Lemma to a multidimensional state requires some additional assumptions. Assume

(1) $\mathbf{W}(t) = [W_1(t), \ldots, W_n(t)]$ is an n-dimensional Brownian motion. Each W_i can be, but is not necessarily independent from every other W_i.
(2) $\mathbf{G}(t)$ is an $\mathbb{M}^{n\times m}$ valued stochastic process, meaning for each input t, an $n \times m$ matrix of random variables is the output.
(3) $\mathbf{F}(t)$ is an $\mathbb{R}^n$ valued stochastic process. For each input (t), a vector of length n of random variables is the result.
(4) $\mathbf{F}$ and $\mathbf{G}$ are in the spaces $\left[\mathbb{L}^1([0,T])\right]^n$ and $\left[\mathbb{L}^2([0,T])\right]^{n\times m}$ respectively. This means that for each index chosen, the individual process that generates the value for that index is in the one dimensional $\mathbb{L}$-space.

Then we can say that an $\mathbb{R}^n$ valued stochastic process $\mathbf{X}(t) = [X_1(t), \ldots, X_n(t)]$ over the time interval $[0, T]$ satisfying the property

$$\mathbf{X}(s) - \mathbf{X}(r) = \int_r^s \mathbf{F}dt + \int_r^s \mathbf{G}dW \tag{33}$$

with $s, r \in [0, T]$, $\mathbf{F} \in [\mathbb{L}^1([0, T])]^n$, and $\mathbf{G} \in [\mathbb{L}^2([0, T])]^{n\times n}$ has the stochastic differential

$$d\mathbf{X} = \mathbf{F}dt + \mathbf{G}d\mathbf{W} \tag{34}$$

which means that

$$dX_i = F_i dt + \sum_{j=1}^{m} G_{i,j} dW_j \qquad i = 1, \ldots, n. \tag{35}$$

With these definitions in mind, we can state Ito's Lemma for **n**-dimensional stochastic processes.

THEOREM 3.4.2 (Ito's Lemma in n dimensions). *Suppose that* $\mathbf{X}$ *is a stochastic process with differential*

$$d\mathbf{X} = \mathbf{F}dt + \mathbf{G}d\mathbf{W} \tag{36}$$

where $\mathbf{F} \in \left[\mathbb{L}^2([0, T]\right]^n$ *and* $\mathbf{G} \in \left[\mathbb{L}^2([0, T])\right]^{n\times m}$. *Assume that a function* $u : \mathbb{R}^n \times [0, T] \to \mathbb{R}^n$ *is continuous with continuous first order partial derivatives* $\frac{\partial u}{\partial x_i}(i = 1, ..., n)$ *and continuous second order partial derivatives* $\frac{\partial^2 u}{\partial x_i \partial x_j}(i, j = 1, \ldots, n)$. *Then*

$$d(u(\mathbf{X}(t), t)) = \frac{\partial u}{\partial t}dt + \sum_{i=1}^{n} \frac{\partial u}{\partial x_i} dX_i + \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n} \frac{\partial^2 u}{\partial x_i \partial x_j} \sum_{l=1}^{m} G_{i,l}G_{j,l} \tag{37}$$

The proof follows a very similar line of reasoning as the one dimensional formula and will not be discussed here. Instead, see [**12**] for further details.

3.5. The Fokker-Planck Equation

Solving stochastic differential equations can be difficult at times, while solving ordinary differential and partial differential equations is a field of study with a much broader base. Therefore, if we can reduce a stochastic differential equation to a partial differential equation, we may be able to gain additional insight into the behavior of the SDE.

The concept that draws the connection between the PDE and the SDE is the notion of the probability density of a stochastic process. As in the discussion of Ito's Lemma, if we are dealing with a function of time and a stochastic process, the probability density will also be a function of time and the values the stochastic process takes on. Before we begin, it is important to distinguish between a stochastic process $X(t)$ and its probability density $p(x, t)$. We know that at any given time t for which the stochastic process X is defined, evaluating X at t results in a random variable. The probability density, $p(x, t)$ at this same time t gives the distribution of the random variable $X(t)$.

Now, if we consider the stochastic differential equation

$$dX = Fdt + GdW \tag{38}$$

and the function

$$Y(t) = u(X(t), t) \tag{39}$$

with the following conditions:

$$\begin{aligned} u, \tfrac{\partial u}{\partial t}, \tfrac{\partial u}{\partial x}, \tfrac{\partial^2 u}{\partial x^2} &\in \mathbb{C}_0^\infty(\mathbb{R}) \\ F &\in \mathbb{L}^1[0, T] \\ G &\in \mathbb{L}^2[0, T] \end{aligned} \tag{40}$$

where $\mathbb{C}_0^\infty(\mathbb{R})$ is the space of continuous functions with an arbitrarily large number of continuous derivatives that tend to zero at infinity, then we know that from Ito's Lemma:

$$\begin{aligned} dY &= \tfrac{\partial u}{\partial t}dt + \tfrac{\partial u}{\partial x}dX + \tfrac{1}{2}\tfrac{\partial^2 u}{\partial t^2}G^2 dt \\ &= \left(\tfrac{\partial u}{\partial t} + \tfrac{\partial u}{\partial x}F + \tfrac{1}{2}\tfrac{\partial^2 u}{\partial x^2}G^2\right)dt + \tfrac{\partial u}{\partial x}G dW \end{aligned} \tag{41}$$

If we apply our understanding of the stochastic differential to these terms and recall that the expected value of a process integrated with respect to dW is 0, the following is a result of taking the expected value of both sides of the equation for Y:

$$\frac{d\mathbb{E}[Y]}{dt} = \mathbb{E}\left[\frac{\partial u}{\partial t} + \frac{\partial u}{\partial x}F + \frac{1}{2}\frac{\partial^2 u}{\partial x^2}G^2\right] \tag{42}$$

Defining the probability distribution $p(x,t)$ of the stochastic process X as above and replacing the expected value term with its definition results in

$$\frac{d}{dt}\int_{-\infty}^{\infty} p(x,t)u(x,t)dx = \int_{-\infty}^{\infty} p(x,t)\left(\frac{\partial u}{\partial t} + \frac{\partial u}{\partial x}F + \frac{1}{2}\frac{\partial^2 u}{\partial x^2}G^2\right)dx \tag{43}$$

Rearranging the equation and changing some notation simplifies it slightly

$$\int_{-\infty}^{\infty}\left(\frac{\partial(pu)}{\partial t} - p\frac{\partial u}{\partial t} - pF\frac{\partial u}{\partial x} - \frac{1}{2}pG^2\frac{\partial^2 u}{\partial x^2}\right)dx = 0 \tag{44}$$

Integration by parts yields the following

$$\begin{aligned} p\frac{\partial u}{\partial t} &= \frac{\partial(pu)}{\partial t} - u\frac{\partial p}{\partial t} \\ \int_{-\infty}^{\infty} pF\frac{\partial u}{\partial X}dx &= upF|_{-\infty}^{\infty} - \int_{-\infty}^{\infty} u\frac{\partial(pF)}{\partial X}dx \\ \int_{-\infty}^{\infty} pG^2\frac{\partial^2 u}{\partial X^2}dx &= -u\frac{\partial(pG^2)}{\partial X}\Big|_{-\infty}^{\infty} + \int_{-\infty}^{\infty} u\frac{\partial(pG^2)}{\partial X^2}dx \end{aligned} \tag{45}$$

Since u and $\frac{\partial u}{\partial x} \in \mathbb{C}_0^\infty(\mathbb{R})$, when evaluated at infinity, they are zero. With these facts in mind, we can further reduce the above to

$$\int_{-\infty}^{\infty} u\left(\frac{\partial p}{\partial t} + \frac{\partial(pF)}{\partial X} - \frac{1}{2}\frac{\partial^2(pG^2)}{\partial X^2}\right)dx = 0 \tag{46}$$

As the above equation will hold true for every $u \in \mathbb{C}_0^\infty(\mathbb{R})$, this implies that

$$\frac{\partial p(x,t)}{\partial t} = -\frac{\partial(p(x,t)F(x,t))}{\partial x} + \frac{1}{2}\frac{\partial^2(p(x,t)G^2(x,t))}{\partial x^2}. \tag{47}$$

This final equation is known as the forward Kolmogorov (or Fokker-Planck) equation for probability distributions of solutions to stochastic differential equations. This particular equation is one-dimensional. More generally, we have the multi-dimensional equation as follows, with the following stipulations:

(1) $\mathbf{W}(t)$ is an n-dimensional Brownian motion
(2) $\mathbf{G}(t)$ is an $\mathbb{M}^{n\times m}$ real valued stochastic process
(3) $\mathbf{F}(t)$ is an $\mathbb{R}^n$ valued stochastic process
(4) $\mathbf{F}$ and $\mathbf{G}$ are in the spaces $[\mathbb{L}^1([0,T])]^n$ and $[\mathbb{L}^2([0,T])]^{n\times m}$ respectively.
(5) $p(x,t)$ is the probability distribution at time t for the stochastic differential $d\mathbf{X} = \mathbf{F}dt + \mathbf{G}d\mathbf{W}_t$.

Then p satisfies the following partial differential equation:

$$\frac{\partial p(x,t)}{\partial t} = -\sum_{i=1}^{n}\frac{\partial}{\partial x}\left[p(x,t)F_i(x,t)\right] + \frac{1}{2}\sum_{i=1}^{n}\sum_{j=1}^{n}\frac{\partial^2}{\partial x^2}\left[p(x,t)\sum_{k=1}^{n}G_{ik}G_{jk}\right] \tag{48}$$

With sufficient computing power, and a well-structured numerical method, this equation would allow us to supersede the Monte Carlo simulations for determining the end probability density of three component SDE. However, since it would require large amounts of computing power and another programming language, this particular method of solution was bypassed.

CHAPTER 4

Stochastic Modeling

4.1. Creating the Stochastic Model

In the previously described birth death model, a differential equation was derived. From this differential equation, we were able to create a stochastic model. This was done by noting that when a discrete walk of the population is known, the infinitesimal expected value and second moment of the change of state matrix provide the drift and variance terms included in the stochastic differential equation. In this section, we present the analogous derivation for (3CM).

4.1.1. State Changes and Probability. Recall the three component model:

$$\text{(3CM)} \qquad \begin{cases} \dfrac{dT}{dt} = \lambda - \mu T - kTV \\ \dfrac{dI}{dt} = kTV - \delta I \\ \dfrac{dV}{dt} = pI - cV \end{cases}$$

The first step in creating a stochastic version of this model is to discretize the system. This is done using random walks on the state space of values of T, I, and V. We start by defining three discrete random walks that correspond to the populations: $T(t)$ will refer to a random walk on the population of healthy T-cells, $I(t)$ will refer to a random walk on the population of infected T-cells, and $V(t)$ will refer to a random walk on the virus population. Since we are imposing a discrete-valued model, each of the populations must take on a non-negative integer value, and all changes across any time interval Δt will be an integer. If we shrink Δt sufficiently, then we can assume that over the time period Δt, only one state change occurs, and that state change will alter the populations by $+1, -1$ or 0.

It is rather simple to list the possible state changes of the vector $[T(t), I(t), V(t)]^T$ and match them with their respective biological meaning. Each state change will be denoted by $\Delta S_i = [a, b, c]^T$, where a, b, and c take values of either $+1, -1$ or 0. The following table gives all the possible state changes, their value, and their biological interpretation:

ΔS_i	$[a, b, c]^T$	Biological Interpretation
ΔS_1	$[1, 0, 0]^T$	Production of a Healthy T-cell
ΔS_2	$[-1, 0, 0]^T$	Death of a Healthy T-cell
ΔS_3	$[-1, 1, 0]^T$	Infection of a Healthy T-cell
ΔS_4	$[0, -1, 0]^T$	Death of an Infected T-cell
ΔS_5	$[0, 0, 1]^T$	Production of a Virus
ΔS_6	$[0, 0, -1]^T$	Destruction of a Virus
ΔS_0	$[0, 0, 0]^T$	No Change

In a manner similar to that of the birth-death model given earlier, each of these possible state changes has an associated probability, derived from the differential equations of the three component model. They are given as follows:

ΔS_i	p_i
ΔS_1	$\lambda \Delta t$
ΔS_2	$\mu T(t) \Delta t$
ΔS_3	$kT(t)V(t)\Delta t$
ΔS_4	$\delta I(t) \Delta t$
ΔS_5	$pI(t)\Delta t$
ΔS_6	$cI(t)\Delta t$
ΔS_0	$1 - \sum_{i=1}^{6} p_i$

4.1.2. Expected Value and Second Moment. It is known that the expected value of a random variable is given by the average of each of the possible values the variable can assume, weighted by their corresponding probabilities. If there are n possible events, and the probability of event Y_i is p_i, then $\mathbb{E}[Y] = \sum_{i=1}^{n} p_i Y_i$. In this case, it is necessary to find the expected value of the change of state vector, and we do this below. Note that similar to the calculation in the birth-death process, there are parallels between the expected value and the ordinary differential equation. If we divide by Δt in the expected value, we have a term that looks like the derivative $\frac{dX}{dt}$ on the left, while the right sides of the equations are the same.

$$\mathbb{E}[\Delta S | T(t) = \alpha, I(t) = \beta, V(t) = \gamma] = \sum_{i=0}^{6} p_i \Delta S_i = \begin{bmatrix} \lambda - \mu\alpha - k\alpha\gamma \\ k\alpha\gamma - \delta\beta \\ p\beta - c\gamma \end{bmatrix} \Delta t \tag{49}$$

The second moment matrix, which measures how closely each variable in the system changes with respect to each other, is given in a similar way to the expected value:

$$\mathbb{E}\left[(\Delta S)(\Delta S)^T\right] = \sum_{i=0}^{6} p_i (\Delta S_i)(\Delta S_i)^T \tag{50}$$

As calculated from the values given above:

$$\mathbb{E}\left[(\Delta S)(\Delta S)^T | T(t) = \alpha, I(t) = \beta, V(t) = \gamma\right] = \begin{bmatrix} \lambda + \mu\alpha + k\alpha\gamma & -k\alpha\gamma & 0 \\ -k\alpha\gamma & k\alpha\gamma + \delta\beta & 0 \\ 0 & 0 & p\beta + c\gamma \end{bmatrix} \Delta t \tag{51}$$

4.1.3. Cholesky Factorization. The second moment is included in the stochastic model under a square root, so it is necessary to compute the matrix equal to $(\mathbb{E}\left[(\Delta S)(\Delta S)^T | T(t) = \alpha, I(t) = \beta, V(t) = \gamma\right])^{\frac{1}{2}}$. In this case, we used a method of factorization known as the *Cholesky Factorization.*

THEOREM 4.1.1 (Cholesky Factorization). *A real, symmetric matrix* $\boldsymbol{A}$ *is positive definite if and only if* $\boldsymbol{A}$ *can be decomposed into* $\boldsymbol{A}=\boldsymbol{L}\boldsymbol{L}^{\boldsymbol{T}}$*, where* $\boldsymbol{L}$ *is a unique, real, lower triangular matrix with strictly positive diagonal entries.*

Computationally, this matrix is not difficult to find. We know that L is of the form:

$$L = \begin{bmatrix} l_{1,1} & 0 & 0 \\ l_{2,1} & l_{2,2} & 0 \\ l_{3,1} & l_{3,2} & l_{3,3} \end{bmatrix} \tag{52}$$

Therefore,

$$\begin{aligned}\mathbb{E}\left[(\Delta S)(\Delta S)^T|T(t)=\alpha, I(t)=\beta, V(t)=\gamma\right] &= LL^T \\ &= \begin{bmatrix} l_{1,1} & 0 & 0 \\ l_{2,1} & l_{2,2} & 0 \\ l_{3,1} & l_{3,2} & l_{3,3} \end{bmatrix} \begin{bmatrix} l_{1,1} & l_{2,1} & l_{3,1} \\ 0 & l_{2,2} & l_{3,2} \\ 0 & 0 & l_{3,3} \end{bmatrix} \\ &= \begin{bmatrix} (l_{1,1})^2 & l_{1,1}l_{2,1} & l_{1,1}l_{3,1} \\ l_{2,1}l_{1,1} & (l_{2,1})^2+(l_{2,2})^2 & l_{2,1}l_{3,1}+l_{2,2}l_{3,2} \\ l_{3,1}l_{1,1} & l_{3,1}l_{2,1}+l_{3,2}l_{2,2} & (l_{3,1})^2+(l_{3,2})^2+(l_{3,3})^2 \end{bmatrix}\end{aligned}$$

If we make the following change of variables from the variance matrix

$$\begin{aligned}\mathbb{E}\left[(\Delta S)(\Delta S)^T|T(t)=\alpha, I(t)=\beta, V(t)=\gamma\right] &= \begin{bmatrix} \lambda+\mu\alpha+k\alpha\gamma & -k\alpha\gamma & 0 \\ -k\alpha\gamma & k\alpha\gamma+\delta\beta & 0 \\ 0 & 0 & p\beta+c\gamma \end{bmatrix} \\ &=: \begin{bmatrix} x & y & 0 \\ y & z & 0 \\ 0 & 0 & w \end{bmatrix}\end{aligned}$$

then we arrive at the following equations

$$\begin{aligned} (l_{1,1})^2 &= x & l_{2,1}l_{1,1} &= y \\ (l_{2,1})^2+(l_{2,2})^2 &= z & l_{3,1}l_{1,1}) &= 0 \\ l_{3,1}l_{2,1}+l_{3,2}l_{2,2} &= 0 & (l_{3,1})^2+(l_{3,2})^2+(l_{3,3})^2 &= w. \end{aligned}$$

These equations reduce to

$$\begin{aligned} l_{1,1} &= \sqrt{x} & l_{3,1} &= 0 \\ l_{2,1} &= \frac{y}{\sqrt{x}} & l_{3,2} &= 0 \\ l_{2,1} &= \sqrt{z-\frac{y^2}{x}} & l_{3,3} &= \sqrt{w} \end{aligned}$$

This leads to the lower triangular matrix

$$L = \begin{bmatrix} \sqrt{\lambda+\mu\alpha+k\alpha\gamma} & 0 & 0 \\ \frac{-k\alpha\gamma}{\sqrt{\lambda+\mu\alpha+k\alpha\gamma}} & \sqrt{(k\alpha\gamma+\delta\beta)-\frac{(-k\alpha\gamma)^2}{\lambda+\mu\alpha+k\alpha\gamma}} & 0 \\ 0 & 0 & \sqrt{p\beta+c\gamma} \end{bmatrix}$$

With this lower triangular matrix and the derivation of its component parts, we can now efficiently calculate the square root of the second moment matrix. This added efficiency allows us to run more simulations effectively and produce better results.

4.2. A SDE based on the Discrete Model

Before we can model a stochastic process for HIV, we must first rigorously define such a process and prove it to be representative of this biological phenomena. We already have a clear idea of the situation we seek to model. This comes from the discrete model shown earlier; therefore, we base the properties of the stochastic model on the properties of the discrete model.

Recall from the previous section that at time t, the state change ΔS possesses the following two properties:

(1) $\mathbb{E}[\Delta S|T(t)=\alpha, I(t)=\beta, V(t)=\gamma] = \begin{bmatrix} \lambda-\mu\alpha-k\alpha\gamma \\ k\alpha\gamma-\delta\beta \\ p\beta-c\gamma \end{bmatrix}$

$$(2)\ \ \mathbb{E}\left[(\Delta S)(\Delta S)^T | T(t)=\alpha, I(t)=\beta, V(t)=\gamma\right] = \begin{bmatrix} \lambda+\mu\alpha+k\alpha\gamma & -k\alpha\gamma & 0 \\ -k\alpha\gamma & k\alpha\gamma+\delta\beta & 0 \\ 0 & 0 & p\beta+c\gamma \end{bmatrix}$$

We desire to create a stochastic process with the same properties.

4.2.1. Infinitesimal Mean and Second Moment. From [**16**], we know that we can create a stochastic differential equation for the three component model from the discrete model by using the infinitesimal means as the coefficients for the dt or "drift" term and using the second moment for the dW_t or "diffusion" terms.

In the previous section, we calculated the expected value, or mean and the second moment of the discrete model. From this point, based on the results of Tuckwel and LeCorfec [**16**], we can use the infinitesimal mean and second moment to generate a stochastic differential equation. These infinitesimal mean and second moment are computed by taking the standard mean and second moment calculations, than dividing by Δt and taking the limit as Δt goes to zero. In this way, they are computed over an "infinitesimally small" period of time.

Recall that the mean was:

$$\mathbb{E}[\Delta S | T(t)=\alpha, I(t)=\beta, V(t)=\gamma] = \sum_{i=0}^{6} p_i \Delta S_i = \begin{bmatrix} \lambda-\mu\alpha-k\alpha\gamma \\ k\alpha\gamma-\delta\beta \\ p\beta-c\gamma \end{bmatrix} \Delta t \tag{53}$$

Dividing by Δt and taking the limit as Δt goes to zero gives us the infinitesimal mean:

$$\lim_{\Delta t\to 0} \frac{\mathbb{E}[\Delta S | T(t)=\alpha, I(t)=\beta, V(t)=\gamma]}{\Delta t} = \sum_{i=0}^{6} p_i \Delta S_i = \begin{bmatrix} \lambda-\mu\alpha-k\alpha\gamma \\ k\alpha\gamma-\delta\beta \\ p\beta-c\gamma \end{bmatrix} \tag{54}$$

Similarly with the second moment matrix, we can calculate the infinitesimal second moment to be:

$$\lim_{\Delta t\to 0} \frac{\mathbb{E}\left[(\Delta S)(\Delta S)^T | T(t)=\alpha, I(t)=\beta, V(t)=\gamma\right]}{\Delta t} = \begin{bmatrix} \lambda+\mu\alpha+k\alpha\gamma & -k\alpha\gamma & 0 \\ -k\alpha\gamma & k\alpha\gamma+\delta\beta & 0 \\ 0 & 0 & p\beta+c\gamma \end{bmatrix} \tag{55}$$

4.2.2. Piecing Together the Stochastic Differential Equation. Since we know stochastic differential equations are of the form

$$dX(t) = F(X,t)dt + G(X,t)dW_t$$

Where F is the infinitesimal expected value of the state change and G is the infinitesimal second moment, we have the stochastic differential equation for the three component model:

$$\begin{aligned} d\begin{bmatrix} T \\ I \\ V \end{bmatrix} &= \begin{bmatrix} \lambda-\mu T-kTV \\ kTV-\delta I \\ pI-cV \end{bmatrix} dt \\ &\quad + \begin{bmatrix} \sqrt{\lambda+\mu T+kTV} & 0 & 0 \\ \frac{-kTV}{\sqrt{\lambda+\mu T+kTV}} & \sqrt{(kTV+\delta I)-\frac{(-kTV)^2}{\lambda+\mu T+kTV}} & 0 \\ 0 & 0 & \sqrt{pI+cV} \end{bmatrix} dW_t \end{aligned}$$

This also allows us to state the multidimensional Fokker-Planck Equation for the stochastic three component model. Since we know that **F** and **G** satisfy

$$\mathbf{F} = \begin{bmatrix} \lambda-\mu T-kTV \\ kTV-\delta I \\ pI-cV \end{bmatrix} \qquad \mathbf{G} = \begin{bmatrix} \lambda+\mu T+kTV & -kTV & 0 \\ -kTV & kTV+\delta I & 0 \\ 0 & 0 & pI+cV \end{bmatrix} \tag{56}$$

we find from the first half of the equation

$$\sum_{i=1}^{3} \mathbf{F}_i(X,t) = (\lambda - \mu T - \delta I + pI - cV) \tag{57}$$

From the second, if we make the following substitutions for $\mathbf{G}$

$$\mathbf{G} = \begin{bmatrix} \lambda + \mu T + kTV & -kTV & 0 \\ -kTV & kTV + \delta I & 0 \\ 0 & 0 & pI + cV \end{bmatrix} = \begin{bmatrix} a & c & 0 \\ c & b & 0 \\ 0 & 0 & d \end{bmatrix}$$

then we see

$$\begin{aligned} \sum_{i=1}^{3}\sum_{j=1}^{3}\sum_{k=1}^{3} \mathbf{G}_{ik}\mathbf{G}_{jk} &= (a+c)^2 + (b+c)^2 + d^2 \\ &= (\lambda + \mu T + kTV - kTV)^2 + (kTV + \delta I - kTV)^2 + (pI + cV)^2 \\ &= (\lambda + \mu T)^2 + (\delta I)^2 + (pI + cV)^2 \\ &= \lambda^2 + 2\lambda\mu T + (\mu T)^2 + (\delta I)^2 + (pI)^2 + 2(pcIV) + (cV)^2 \end{aligned}$$

With all of this in mind, we can write the multi dimensional Fokker-Planck equation for the stochastic Three Component Model:

$$\begin{aligned} \frac{\partial p(x,t)}{\partial t} &= -\frac{\partial}{\partial x}\left[p(x,t)(\lambda - \mu T - \delta I + pI - cV)\right] \\ &\quad + \frac{1}{2}\frac{\partial^2}{\partial x^2}\left[p(x,t)(\lambda^2 + 2\lambda\mu T + (\mu T)^2 + (\delta I)^2 + (pI)^2 + 2(pcIV) + (cV)^2\right] \end{aligned}$$

4.3. Existence and Uniqueness of Solutions to SDEs

The end goal of crafting the SDE is to find the solution to the stochastic differential equation, or at the very least, identify its important properties. Since our model is nonlinear, it's quite difficult to obtain an analytic representation of a solution, if one even exists, so we resort to computational means in order to calculate sample paths of solutions. Regardless of how we attempt to obtain a solution, it is important to verify that the solution we are searching for exists and is unique. For this, we can use theorems from Øksendal [**12**] and Mao [**11**].

THEOREM 4.3.1 (Mao). *Assume that the stochastic process $X(t)$ satisfies*

$$dX(t) = f(t, X(t))dt + g(t, X(t))dW_t \tag{58}$$

with the given initial condition $X(0) = X_0 \in \left[\mathbb{L}^2(\mathbb{R}^d)\right]^n$, where f and g satisfy the following conditions for some $T > 0$:

(1) (Local Lipschitz) There exists $C > 0$ and a compact $K \subset \mathbb{R}^d$ such that for all $t \in [0,T]$ and all $x, y \in K$

$$\max\left\{|f(t,x) - f(t,y)|^2, |g(t,x) - g(t,y)|^2\right\} \leq C|x-y|^2$$

(2) (Stochastic Monotonicity) There exists $C > 0$ such that for all $(t,x) \in [0,T] \times \mathbb{R}^d$ such that

$$x^T f(t,x) + \frac{1}{2}|g(t,x)|^2 \leq C(1 + |x|^2).$$

Then, there exists a unique solution $X(t)$ to (58) in $\left[\mathbb{L}^2([0,T];\mathbb{R}^d\right]^n$

For the SDE that we have derived and stated at the end of the previous section, the quadratic nature of the first and second moments and bounds from the previous chapter allow f and g to satisfy both the local Lipschitz condition and the Stochastic Monotonicity condition. Hence, we are guaranteed the existence of a unique solution on *some* time interval, though we do not control the extent of time over which the solution is known to exist. A more difficult question that remains unanswered is the global existence of this solution. That is, can this solution be continued to an arbitrarily large time interval, say $[0,T]$ for *any* $T > 0$, or is

their a maximal time of existence? This question is, unfortunately, far outside the scope of the thesis, and hence we will not pursue it further.

Of course, from a modeling or applications perspective, explicitly determining the solution would be much more helpful and provide an enormous amount of information. Since tools for deriving such solutions for SDEs of our type are not known, we proceed instead by computing solutions numerically. The next chapter, then, focuses on numerical methods for approximating solutions to stochastic differential equations, and more specifically, our three-dimensional stochastic model.

CHAPTER 5

Numerical Methods

5.1. Numerical Methods of Computation

Solutions to stochastic differential equations are difficult, if not mathematically impossible to determine. Thus, extended amounts of computation must be done in order to calculate the solution. Methods exist to approximate solutions to these equations, both over intervals of time and at specific points of time. One of the most basic ones is Euler's Method. This particular method is part of a larger group of methods of approximations known as finite difference methods.

5.1.1. Euler's Method. Euler's method is a way of solving differential equations with specific initial values. Consider a function, x over the time interval $[t_0, t_f]$, with its derivative, x', expressed as a function of x and time: $x' = f(t, x(t))$ and an initial value, $x(t_0) = x_0$. Then divide up the time interval into n steps of size h, such that $t_k = t_0 + kh$ and $t_f = t_0 + nh$ Then for each step, $x(t_{k+1})$ can be approximated by $x(t_k) + h \cdot f(t_k, x(t_k))$.

At the end of this these calculations, the error between the actual value of the function and the computed value of the function is proportional to the step size, h. Therefore, decreasing h will decrease the error by a proportional amount. However, doing so will increase the number of computations necessary to complete the method over the entire time interval. Considering the time for each calculation is typically on the order of seconds, a slight increase in time required might not seem like a significant issue. However, when the same calculation is required for hundreds or thousands of trials, the impact grows that much larger.

5.1.2. Discretization of the System. Suppose we have a system of n stochastic differential equations given by

$$d\mathbf{X} = [dX_1, \ldots, dX_n]^T = [f_1(t, X_1(t), \ldots, X_n(t)), \ldots, f_n(t, X_1(t), \ldots, X_n(t))]^T$$

with the initial conditions

$$\mathbf{X}(0) = [X_1(0), \ldots, X_n(0)]^T,$$

and we desire to model the system and acquire a solution for the time interval $[0, T]$. The first step would be to discretize time. Suppose our desire for accuracy of the model within the constraints of the system lead us to require k time steps. We are then left with the sequence of time values $t_0 = 0, t_1 = \frac{T}{k}, t_2 = \frac{2T}{k} \ldots, t_k = T$. A commonly used notation is to define $\Delta t := \frac{T}{k}$, so the sequence of time values becomes $t_0 = 0, t_1 = \Delta t, t_2 = 2\Delta t \ldots, t_k = k\Delta t$.

From here, it is a simple matter to calculate the vector

$$d\mathbf{X}_0 = [f_1(0, X_1(0), \ldots, X_n(0)), \ldots, f_n(0, X_1(0), \ldots, X_n(0))]^T.$$

The approximation for $\mathbf{X}(t_1)$ is given by $\mathbf{X}(t_1) = \mathbf{X}(t_0) + \Delta t \cdot d\mathbf{X}_0$. With $\mathbf{X}(t_1)$ now known, we repeat the process for

$$d\mathbf{X}_1 = f_1(t_1, x_1(t_1), \ldots, x_n(t_1)), \ldots, f_n(t_1, x_1(t_1), \ldots, x_n(t_1))]^T$$

and use it to calculate $\mathbf{X}(t_2) = \mathbf{X}(t_1) + \Delta t \cdot d\mathbf{X}_1$. This process is repeated through $\mathbf{X}(t_k)$ and the end result is a sequence of vectors $[\mathbf{X}(t_0), \ldots, \mathbf{X}(t_k)]$ corresponding to the given sequence of time values. These values can be plotted to give an idea of what the solution looks like, or used computationally for other purposes.

5.1.3. Application to SDEs. As seen, when we desire to model the solution to an ordinary differential equation, the computations are quite simple and deterministic. Once you go through them once, you can be assured that the same results will occur every time. With a stochastic differential equation, the fundamentals are quite the same. The time interval and function are discretized, and the formula for calculating the next value of the equation from the previous one is exactly the same. However, when the discretized derivative for a stochastic process is calculated, it involves a "dW" term. In the discritized sense, we recall that $dW \approx W(t_{k+1}) - W(t_k)$ and that each difference in W is normally distributed with mean 0 and standard deviation equal to the time difference. Therefore, we know $dW \approx W(t_{k+1}) - W(t_k) \sim N(0, t_{k+1} - t_k)$. Since most computational software includes a pseudo-random number generator, we can calculate a dW whenever its necessary. The end result of one run of Euler's method will then be one sample path of the stochastic process that solves the stochastic differential equation.

The result of solving a stochastic differential equation is a stochastic process, which yields a random variable when evaluated at a given point. Therefore, if we were to run two separate trials of Euler's method for the same SDE, we are very likely to get two entirely different sample paths. It is necessary to run many such trials in order to determine the probability distribution of the process over the entire interval and at a specific point.

5.1.4. Example SDE. The following figure (5.1) is an example of Euler's method applied to the process $Y = W(t)$, with the corresponding SDE $dY = dW$ and initial conditions $Y(0) = 0$. We will consider this over the interval $[0, 1]$ with step size .001. We will use the properties $dW \sim N(0, 0.001)$ to aid in our calculations. The approximation from Euler's method will then be $Y(t_{k+1}) = Y(t_k) + \Delta t \cdot dW$.

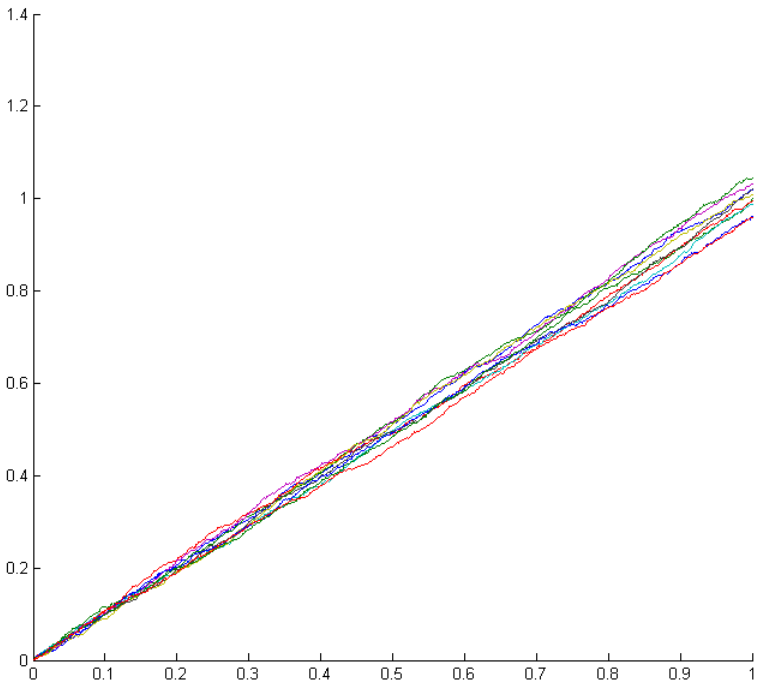


FIGURE 5.1. Plots of Euler's Method with 10 trials

As we can see, the sample paths begin clustered very closely around the line $y = t$, but as time increases they grow more and more spread out, and resemble a normal distribution at the end. (Figure 5.2)

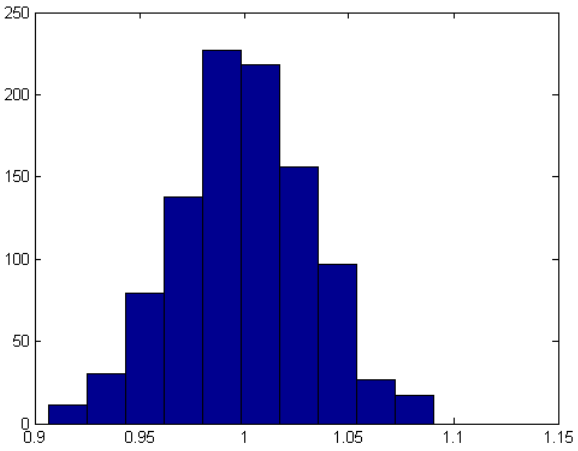


FIGURE 5.2. Histogram of end results with 1000 trials

The time required for this rather simple stochastic process is much greater than for the ordinary Euler's method. Generation of a random variable is a relatively intensive computational task, and requires non-trivial amounts of time.

5.2. Boundary Conditions

When dealing with our particular model for HIV population growth within the human body, we must make some choices regarding our boundary conditions, in order to keep our model in a reasonable realm of biological accuracy.

5.2.1. Definitions. Boundary conditions come into play when the process being modeled nears a bound of the values the process can take on. In our model, these boundaries are drawn from the biological interpretation of the model, specifically, they state that none of the populations can drop below zero. This makes sense, since it is impossible to have negative amounts of a population. Therefore, since the computation of the model does permit the populations to drop below zero, we must find some way of correcting this. In the code, these are triggered with if-statements that come into play when a population goes below zero.

Once the population is negative, there are three ways of dealing with it:

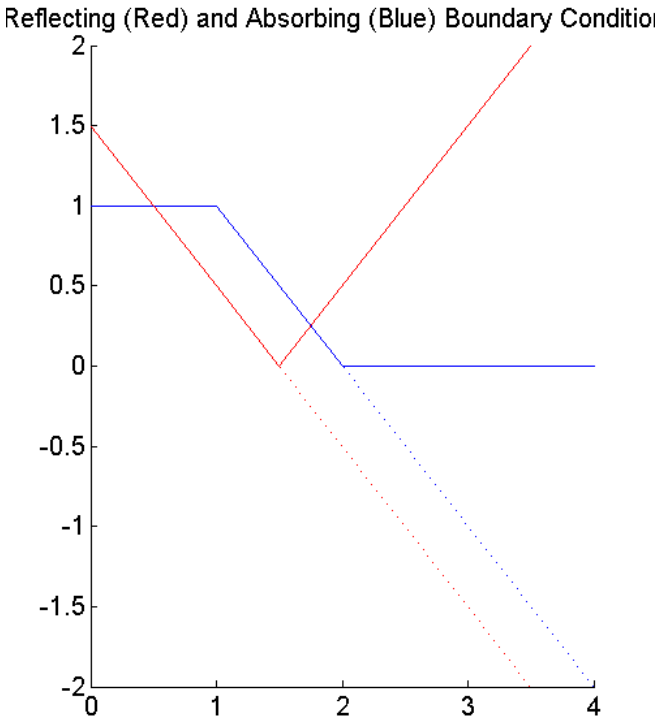
(1) Set the population to the boundary level. These boundary conditions are known as absorbing, since if the population drops below the boundary value, the boundary "absorbs" it.
(2) Set the population to the positive value with the same magnitude as the negative value. These are reflecting boundary conditions, since it is as if the population bounces off the boundary.
(3) Set the population to some random value between the two above options. This is a stochastic boundary condition, since it randomly chooses something between the other two.

5.2.2. Boundary Conditions within the Model. This figure (5.3) demonstrates what these boundary conditions would look like. Suppose we have two paths, red and blue, and we desire to have a boundary at $y = 0$. If we assign to the red path a reflecting boundary, when the path hits the boundary, as opposed to continuing on its path (the dotted line), it returns from the direction it came. At this point, the absolute value of the red solid line and the red dotted line are the same. On the other hand, the blue line has an absorbing boundary condition. When the blue path impacts the boundary, the path takes the boundary value and stays at that point for the remainder of the time.

Coding boundary conditions within the model is not complex, but the behavior of the system can be changed dependent on the type of boundary used. Before delving into the effects the various boundary

conditions have on the system, it is important to note that the T-cell population in the model is never actually allowed to hit zero. Rather, the value `eps` in MATLAB is used. This variable `eps` is short for epsilon, and has a value of approximately 2.2204×10^{-16}. This near zero value is used in place of zero because using zero would, in some cases, result in abnormal behavior in the calculations within the code or cause undesired premature equilibriums in the model.

FIGURE 5.3. Boundary Conditions



When simulating the equations, both reflecting and the modified absorbing boundary conditions were applied in the way described above. The two figures (5.4,5.5) demonstrate the results of each of these runs. The important thing to note in this case is the bimodal distribution of the healthy T-cells in the absorbing boundary condition figure. Some of the population spikes, then drops off rapidly, while another significant amount of the population spikes than slowly fades away. This is in direct contrast to the reflecting boundary conditions, which all see the spike in population, followed by the rapid drop off.

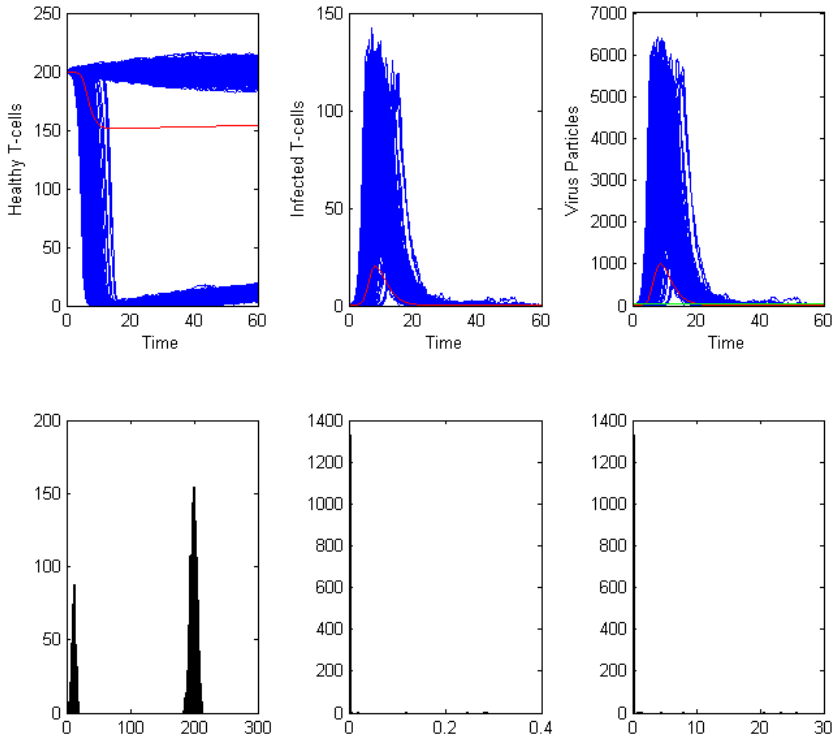


FIGURE 5.4. Plots of 3CM (Absorbing Boundary Conditions)

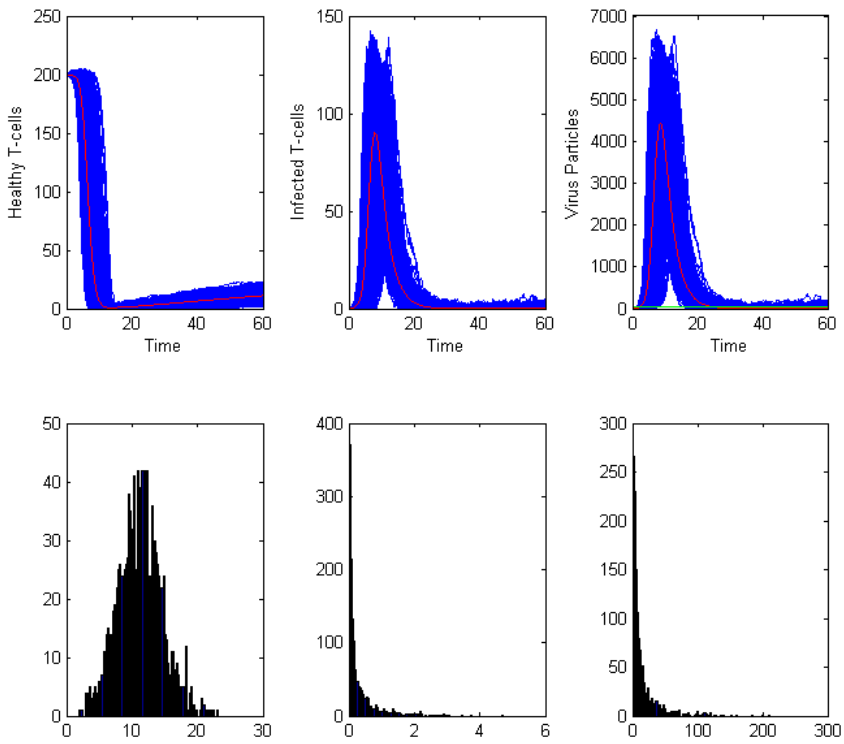


FIGURE 5.5. Plots of 3CM (Reflecting Boundary Conditions)

5.3. Coding the Three Component Model

The simulation of the Three Component Model was developed in MATLAB, and there were several different paths taken to get final probability distributions, and each of them differ in their method of computation.

5.3.1. The Discrete Simulation. This code simulates the discrete model given in the previous section. As with all of the code, the basic idea is to determine how the populations change over a time interval, and run that simulation many times in order to obtain data that can be analyzed in a Monte-Carlo method. We begin here by defining the number of trials, the length of the time interval, and the number of steps across the time interval. We also define the state change vectors. Recall from before that these vectors take the form $[x, y, z]$, where x, y, and z can only take values of $+1$, -1, or 0.

Once these beginning steps are complete, initial conditions are generated for the first trial. From these populations, the probability of each state change vector occurring is calculated. Recall that these probabilities are tied to the differential equation and depend on the population values. Next, a uniform random number from the interval $[0, 1]$ is generated by MATLAB, and scaled to the interval $[0, P]$, where P is the sum of the probabilities. This interval is broken down into subintervals of the form $[0, p_1), [p_1, p_1 + p_2), \ldots, [p_1 + \cdots + p_8, P)$. In this way, the width of each interval is directly proportional to a probability. We determine

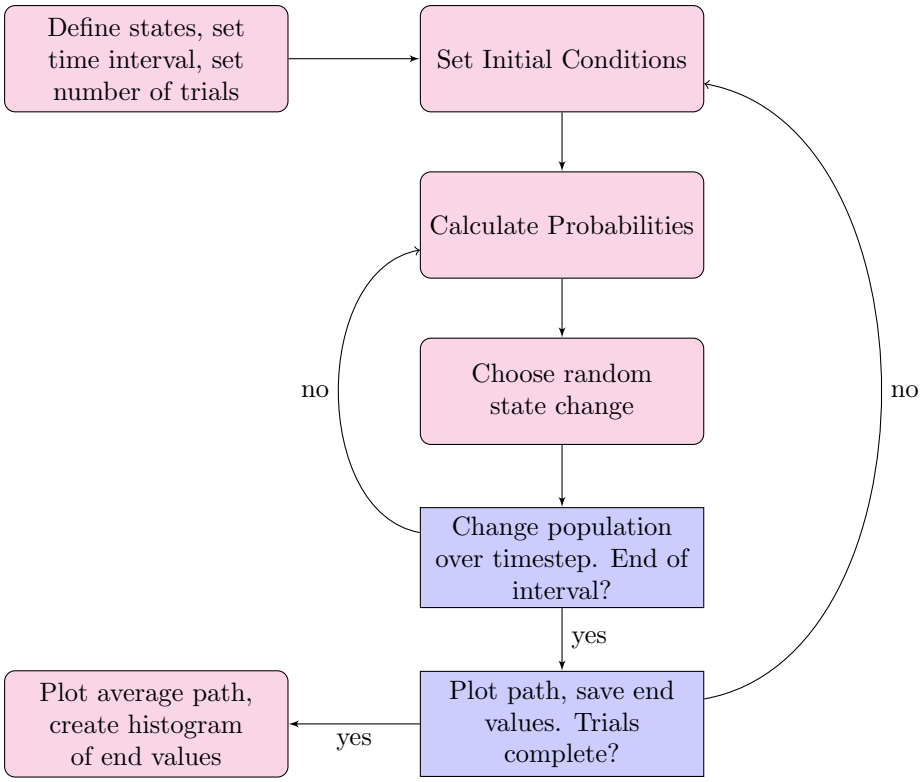


FIGURE 5.6. Flow chart representation of the simulation process

which interval the random number fits into and select the corresponding state change vector to add to the population. This constitutes one time step.

Once the entire time interval has been crossed, the path is plotted and the end values stored. The process is repeated for each trial, and at the end of all of the trials, the average plot is created, as is a histogram of all the end values. In this way, we can determine the percentage of cases in which the end virus level was beneath detectable concentrations.

The flow chart (figure 5.6) gives a general idea of what is being accomplished in the code. Structurally, the code contains two nested $for-$loops, one for the time interval and one for the set of trials.

5.4. Coding Stochastically

Modeling the stochastic version offer advantages not seen in other forms of modeling. Primarily, when we model stochastically, we get to observe the path each trial takes, as opposed to just observing the average path. With this, we get a much better idea of the distribution of paths at a given sample time. The downside, however, is that this modeling is computationally expensive and requires significantly more trials per sample to get acceptable results.

5.4.1. The Basic Stochastic Model. The basic stochastic simulation uses MATLAB to create thousands of sample paths of the populations over time, with each path using the same set of coefficients and initial conditions. The actual code bears more resemblance to the discretized simulation than the deterministic one, due to the method of implementing the simulation. For each sample path, or trial, the time interval is divided in separate intervals. At the endpoint of each interval, the expected change in population is calculated. This expected value change is the exact same as would have been seen in the deterministic model. The stochastic model differs, however, with the addition of a variance term. The variance of the

population change is calculated, and a random vector is generated. The variance matrix is multiplied by the random vector and added to the expected value. This new population change is then added to the old population. Once this entire process has been completed over the entire time interval, it is repeated for a set number of trials. At the end of all the trials, we see the average sample path and the histogram for the end populations.

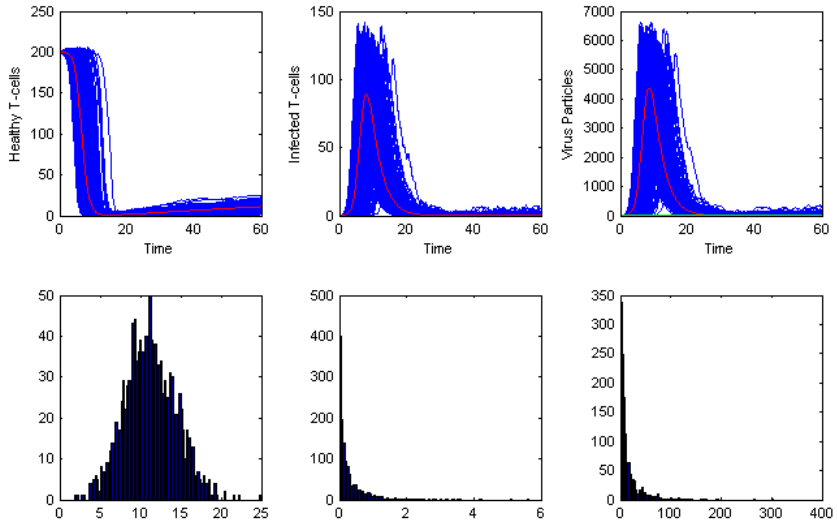


FIGURE 5.7. A simulation of the stochastic model with R=8.18

Again, we note that the green line represents the virus threshold for detection, and that the majority of paths and the average sample path are below that detection threshold. However, it is incredibly important to note that not all sample paths fall below there.

CHAPTER 6

Conclusion

6.1. Results

To conclude the thesis, we will summarize the theoretical, computational, and biological results obtained within. Details can be found in Chapters $2-5$, but for brevity and completeness, we highlight them below.

6.1.1. Theoretical Results. The theorems obtained in previous chapters provide information about the model from a mathematical perspective. In addition to verifying facts necessary to complete the mathematical analysis of the system, these theorems demonstrate that the model is biologically relevant, and remains so for all times, and yield insight into necessary methods of simulation. Below is a brief summary of the main theorems.

THEOREM 1 (Existence and Uniqueness of Solution for the Three Component Model). *Given initial conditions $T(0)$, $I(0)$, and $V(0)$ for the Three Component Model, there exists a unique solution $T(t)$, $I(t)$, and $V(t)$ that satisfies the system of differential equations for all $t \geq 0$ and the given initial conditions.*

This theorem proves that a solution exists for the Three Component Model and that this solution is unique for every unique set of initial conditions. This represents a fundamental step in the analysis of this system of differential equations. While the three component model has been used previously in other studies, no article within the literature proves this fundamental fact.

THEOREM 2 (Positivity of Solution for the Three Component Model). *Given initial conditions $T(0) > 0$, $I(0) >$, and $V(0) > 0$ for the Three Component Model, the unique solution remains bounded for every $t \geq 0$ and possesses the property that $T(t) > 0$, $I(t) > 0$, and $V(t) > 0$ for all $t \geq 0$.*

With the above result, we confirm the biological relevance of the model. This theorem ensures that given positive initial values of each population, the system will evolve so as to preserve this property, and population values will remain positive for all later times. Since negative population values are a biological impossibility - meaning that the number of T-cells or virions within the body should never become negative - the confirmation that this event is also a mathematical impossibility within our model helps verify the relevance of our derivation.

THEOREM 3. *Dependence of the equilibrium on the reproductive constant R Define the reproductive constant, R by*

$$R = \frac{k\lambda p}{c\delta\mu}.$$

The infective equilibrium is stable if and only if $R > 1$. In this case, any solution of the three-component model possesses the property $\lim_{t\to+\infty} V(t) > 0$ and the viral infection is persistent. Conversely, the non-infective equilibrium is stable if and only if $R \leq 1$. In this case, any solution of the three-component model possesses the property $\lim_{t\to+\infty} V(t) = 0$, and the viral infection becomes extinct.

Finally, this last theorem demonstrates that our analysis of the differential equations can be based solely on an analysis of the coefficients, and in particular, the value of a single parameter R. While this is mathematically true, the biological applicability of this statement may fail since it can only be determined that the virus population either persists or becomes extinct as $t \to \infty$. The theorem is unable to tell us at what rate this occurs, or what the values of the viral population are for earlier time periods. One might

guess that eventual extinction should generally imply that the viral population remains small even for small times. However, as we will see, later numerical results indicate that this is not the case.

6.1.2. Numerical Results. Recall that this project simulated the three component model under many different conditions. The results were discussed previously in the thesis, but are listed here for convenience and overview.

Model	Coefficients	Sample Paths	R ≤ 1	$V(60) < 40 \frac{\text{virons}}{\mu\text{L}}$
ODE	Random	10000	211	2140
SDE	Mean Valued	10000	0	1417
SDE	Random	10000	300	2536

TABLE 6.1. Values from the differing simulations of ODE and SDE models

Notice that the proportion of trials within our simulation that resulted in $R \leq 1$ is much smaller - by nearly a factor of ten - than those which resulted in viral populations less than 40 virions per μL approximately two months after the initial infection. Hence, a standard mathematical definition of extinction, namely $\lim_{t\to\infty} V(t) = 0$ which (by Theorem 3) is equivalent to $R < 1$, is insufficient to accurately describe the behavior of the viral population on the timescales of biological relevance, specifically during the time period up to a few months after initial infection. Instead, a more precise determination of viral extinction can be made by measuring whether the virus population will remain below the current detectable threshold of 40 virions per μL, and under this measure, the probability of extinction is much larger. As can be seen by Table 6.1, the probability of extinction by the former measure is only around 2%, while the probability jumps by a factor of ten to approximately $20 - 25\%$ under the latter notion that we have proposed. In some types of transmission, such as passage of the disease from a mother to an unborn child or through needlesticks , this percentage is much closer to current estimates of the probability of extinction after initial infection than the criteria $R \leq 1$.

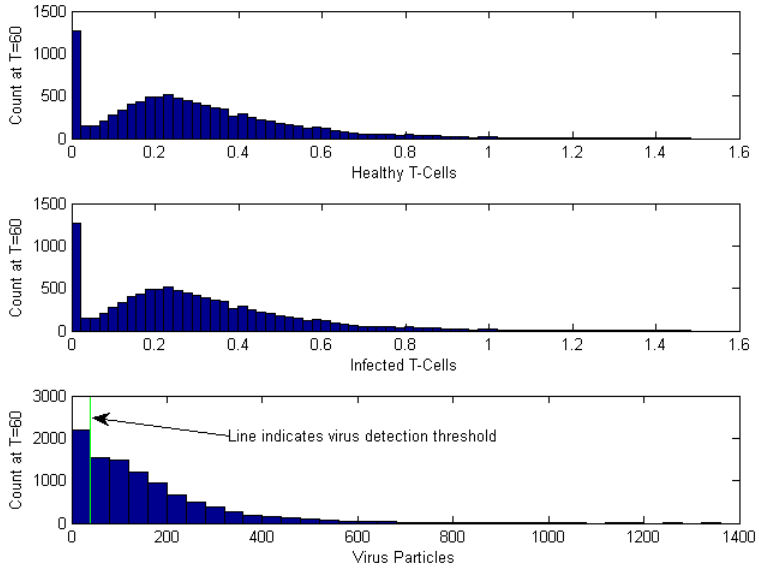


FIGURE 6.1. Histograms of end state values from ODE w/ RV coefficients

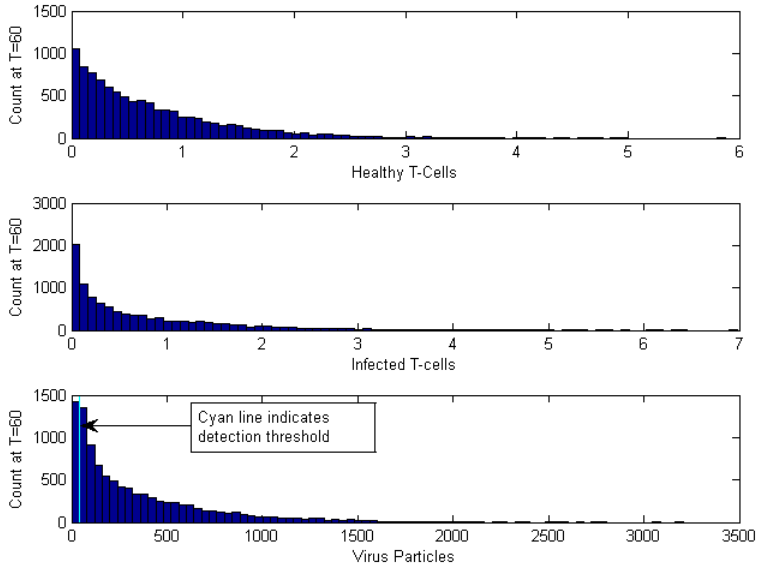


FIGURE 6.2. Histograms of end state values from SDE w/ mean coefficients

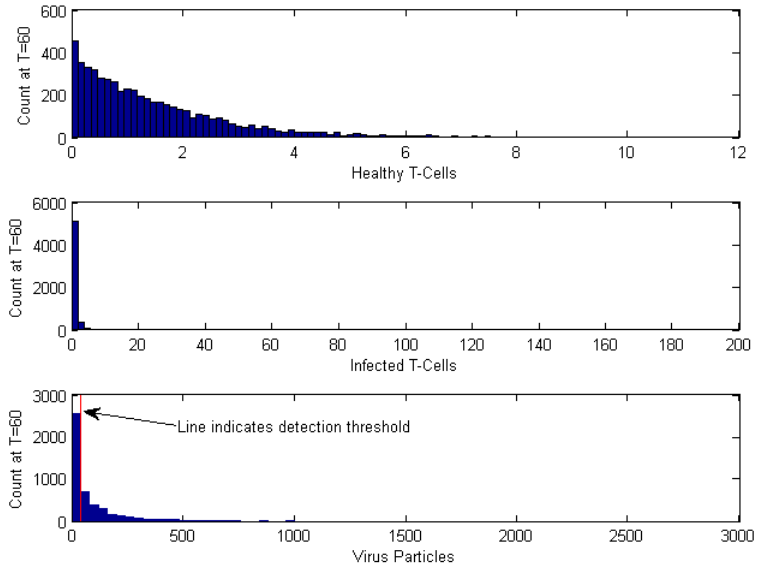


FIGURE 6.3. Histograms of end state values from SDE w/ RV coefficients

The histograms (6.1, 6.2, 6.3) display the end population values for each of the healthy T-cells, infected T-cells, and virions, as described by a particular model. The top set of figures is for the ordinary differential

equations simulated with random variable coefficients, the middle set of figures is for the stochastic differential equation simulated with the mean valued coefficients for each of the parameters, and the final set of histograms is for the stochastic equations simulated with random variable coefficients. There is line drawn on the histograms for the viral populations. All entries to the left of this bar represent those simulations that resulted in the number of virus particles being less than 40 virions per μL. This is, as mentioned before, the biological threshold for persistence.

6.2. Conclusion

Throughout this research, we sought to answer the question: "How does creating a stochastic model alter results obtained from simulating the Three Component Model?" The idea for the question came from Tuckwell and Shipman. They found [**17**] in their simulations of the model of ordinary differential equation that viral persistence happened at a rate of approximately 2 %. This was done by calculating randomly generated R values and counting the number above and below one.

In our work, we did three things. First, we redefined the notion of persistence. We note that the end viral population, $V(60)$, could less than the threshold of detectability permitted by modern science at a much greater rate than expected by the R value. What does this mean? It indicates that the methods used by Tuckwell and Shipman are not as accurate as could be hoped for. It makes clear that a full simulation of the model is required to get accurate data. Therefore, with our second notion of extinction and persistence stemming from a biological perspective, we can carry out the simulations again.

With full simulation of the ordinary differential equations, we discovered that viral persistence happened at a rate of roughly ten times that suggested in [**17**]. This proves rather conclusively that biological persistence and mathematical persistence, while related, are not identical, and simulation is necessary to realize the full implications of the model. In reality, persistence can happen at a rate of up to 90 %, if the virus is transmitted by blood, or around 1 % via intercourse [**5**]. While 2 % from [**17**] seems to be accurate, recall that these coefficients were drawn from people with HIV already, and therefore are biased towards transmission.

Second, we took the mean valued coefficients and simulated the stochastic differential equations for the Three Component Model. These coefficients give us the "average" person, in a sense, and the stochasticity allowed us to simulate this person many times, with slight random variations each time. Based on the coefficients alone, we would expect the virus to persist all of time, but as we demonstrated, a full simulation would be required. In addition to this, the added stochasticity would incorporate the randomness inherent in the external world. The virus persisted most of the time, but far from all of it.

Finally, by combining the first and second methods, we simulated the stochastic model with different sets of coefficients. The results we obtained were similar to those of the first method. Persistence happened nearly eight times more than would be expected from the coefficients alone. This demonstrates that the stochasticity also alters the results of the simulation towards a more realistic end.

Stochastic models tell us more than can be told with models based on ordinary differential equations. We learned that incorporating stochasticity noticeably alters the results we would otherwise expect from simulation. This, coupled with a different notion of persistence shows us we can improve the model to more accurately describe real world conditions.

6.3. Areas of Further Study

Further study could be done in a number of areas. The model could be expanded to include antiretroviral treatment (HAART), or to include such biological phenomena as the latent cell reservoir. These models would then more closely resemble the interaction between the virus and the body. From a more mathematical end, the Fokker-Planck equation described previously with the paper could be solved for the probability density at the end of the model. Additionally, the stochastic differential equations themselves could be studied, and analyzed for their stability and equilibrium. This study was only able to examine existence and uniqueness of solution.

While the first set of proposed extensions describe ways to expand an accurate model of extinction probabilities and the second, methods of expanding purely mathematical knowledge, both would be useful in further efforts to model HIV in its early stages.

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APPENDIX A

Code

A.0.1. Deterministic Code.

ODEs at different coefficient sets:

```
function sol=PopDer(t,P)
    %P represents a vector of initial populations in the form [T, I, V]

lambda = 4.3e-2;
mu = .020;
k = .19e-3;
Δ = .080;
p= 98;
c= 3.81;

sol = [lambda-mu*P(1)-k*P(1)*P(3);k*P(1)*P(3)-Δ*P(2);p*P(2)-c*P(3)];
```

```
function sol=PopDer2(t,P)
    %P represents a vector of initial populations in the form [T, I, V]

lambda = .2;
mu = .0043;
k = 4.8e-3;
Δ = .13;
p= 7100;
c= 2.06;

sol = [lambda-mu*P(1)-k*P(1)*P(3);k*P(1)*P(3)-Δ*P(2);p*P(2)-c*P(3)];
```

Generate figures and statistics from deterministic model:

```
clear
clc
clf

lambda = .11;
mu = .01089;
k = .001179;
Δ = .3660;
p=1426.8;
c=3.074;

R=(k*lambda*p)/(mu*Δ*c)

[t,y]=ode45(@PopDer,[0,60],[200,0,4e-7]);
subplot(2,3,1), plot(t,y(:,1)), xlabel('Time (days)'),ylabel('Healthy T-cells (units?)');
subplot(2,3,2), plot(t,y(:,2)), xlabel('Time (days)'),ylabel('Infected T-cells (units?)');
subplot(2,3,3), plot(t,y(:,3)), xlabel('Time (days)'),ylabel('Virus ...
    (particles/microliter)'), line([0,60],[40,40],'color','r');
[t,y]=ode45(@PopDer2,[0,60],[200,0,4e-7]);
subplot(2,3,4), plot(t,y(:,1)), xlabel('Time (days)'),ylabel('Healthy T-cells (units?)');
subplot(2,3,5), plot(t,y(:,2)), xlabel('Time (days)'),ylabel('Infected T-cells (units?)');
subplot(2,3,6), plot(t,y(:,3)), xlabel('Time (days)'),ylabel('Virus ...
    (particles/microliter)'), line([0,60],[40,40],'color','r');
```

A.0.2. Deterministic Code with RV coefficients.

Generate truncated normal distributions

```
function z = truncatednormal(N,mu,sigma,trunc_low,trunc_high)
% truncatednormal: trncated normal random variable generator
%
% input explanations
% N — size of resultant matrix/array
% mu — mean of untrncated distribution
% sigma — std dev of untruncated distribution
% trunc_low — low truncation point
% trunc_high — high truncated point
%
% output explanation
% z — array of size N of truncated random variables with above properties
%

% set the defaults


% If N is not entered, set the default value of N to be 1
if (nargin <1)|isempty(N)
    N=1;
end

%If no mean is given, set it to be 0
if (nargin < 2)|isempty(mu)
    mu=0;
end

%If no standard deviation is given, set it to be 1
if (nargin < 3)|isempty(sigma)
    sigma=1;
end

%If no low end of truncation is given, set it to be negative infinity
% prob_low is the probability that the the value of the random variable is
% less than the truncation point for the given distribution, if trunc_low is
% empty, set prob_low to be zero
if (nargin < 4)|isempty(trunc_low)
    trunc_low=-inf;
    prob_low=0;
else
    prob_low=normcdf((trunc_low-mu)/sigma);
end

%If no upper end of trunation is given, set it to be infinity
% prob_high is the probability that the value of the random variable is
% less than the truncaion point. If trunc_high is empty, set it to be one.
if (nargin < 5)|isempty(trunc_high)
    trunc_high=inf;
    prob_high=1;
else
    prob_high=normcdf((trunc_high-mu)/sigma);
end

% Test for correct order of truncation points
if trunc_low>trunc_high
```

```
56      error 'Must have trunc_low less than or equal to trunc_high'
57  end
58
59  %Generate a size N standard normal random variable
60  r=rand(N);
61
62  %scale to the interval [plo,phi]
63  r=prob_low+(prob_high-prob_low)*r;
64
65  %Invert using the standard normal
66  z=norminv(r);
67
68  %Rescale and shift using given mean and standard deviation
69  z=mu+sigma*z;
```

Generate coefficient sets

```
function [lambda,mu,k,Δ,p,c] = CoefCreator;
% This function generates random coefficents for use in 3CM.

% We create the random coefficients based on the data from Stafford, et all
% The function "truncatednormal(N,mu,sigma,trunc_low,trunc_high)" generates
% an array of random variables of size N, with mean mu and standard
% deviation sigma, truncated to be in the interval [trunc_low,trunc_high].
% The interval of truncation is given to be [0,inf).


% Here we use the max and min values from Stafford et all as the truncation
% points.


lambda = truncatednormal(1,.1089,.05727,.043,.20);
mu = truncatednormal(1,.01089,.005727,.0043,.020);
k = truncatednormal(1,.001179,.001422,.00019,.00480);
Δ = truncatednormal(1,.3660,.193,.13,.80);
p = truncatednormal(1,1426.8,2049.36,98,2697);
c = truncatednormal(1,3.074,0.64,2.06,3.81);
%c=3;
```

Ordinary Differential Equations:

```
function sol=Det_3CM(t,P,lambda,mu,k,Δ,p,c);

% This function is the ODE for the deterministic 3CM.
% t is time, P is population, coef is the coefficient vector


sol = [lambda-mu*P(1)-k*P(1)*P(3);k*P(1)*P(3)-Δ*P(2);p*P(2)-c*P(3)];
```

Simulate ODE:

```
function Data=ODE_Simulator()

clear
clc
tic

% Determine the number of trials
trials=100;

% Create a holding matrix for the end populations and the R value [T I V R]
Data=zeros(trials,4);

% Determine initial conditions
IC=[200,0,4e-7];

% Initialize trials
for trial=1:trials;


   % Generate Coefficients
   [lambda,mu,k,Δ,p,c] = CoefCreator;

   % Calculate and save R value
   Data(trial,4)=(k*lambda*p)/(c*Δ*mu);


   % Solve the  ODE
   % The output is the matrix with time and solution. The imputs are the
   % function being solved, time span, initial conditions, options, and
   % other inputs to the function.
   [t,y] = ode45(@Det_3CM,[0,100],IC,[],lambda,mu,k,Δ,p,c);


   % Determine how long the solution vector y is
   length_y=length(y);

   % Take the end values of the solution vector to y and store them in data
   Data(trial,[1:3])=y(length_y,:);

   if mod(trial,floor(trials/100))==0
    fprintf('Percent Completed: %f%%, Time Elapsed: %f seconds \n', trial/trials*100, toc)
   end

end
```

Plot ODE:

```
clear
clc
clf

Data=ODE_Simulator;

hold on
subplot(2,2,1), scatter(Data(:,4),Data(:,1)), xlabel('R Value'), ylabel('End T-Cell ...
    Population')
subplot(2,2,2), scatter(Data(:,4),Data(:,2)), xlabel('R Value'), ylabel('End I-Cell ...
    Population')
subplot(2,2,3), scatter(Data(:,4),Data(:,3)), xlabel('R Value'), ylabel('End Virus ...
    Population')
```

A.0.3. Discrete Simulation Code.

```
clear
clc
clf



%Set initial values
T0=10000;
I0=0;
V0=1;
InitialValues=[T0,I0,V0];


%Set Coefficients
lambda = .272;
mu = .00136;
K = .00027;
Δ = .33;
p=100;
c=2;

%Set number of steps
steps=100000;

%Set total time
Time=100;

%Caclulate time interval
t=Time/steps;

%Generate "Storage" Matrix (will be 3x(Steps+1) sized)

Population=zeros(steps+1,3);
Population(1,:)=InitialValues;

%Define State Changes
S1=[1,0,0];
S2=[-1,0,0];
S3=[-1,1,0];
S4=[0,-1,0];
S5=[0,0,1];
S6=[0,0,-1];
S0=[0,0,0];


%Define number of trials;
trials=1000;

%Set storage matricies for average value and end states
Average=zeros(steps+1,3);
EndValues=zeros(trials,3);

%Create a time vector for plotting purposes
time=[0:t:Time];


```

```
57 for trial=1:trials;
58
59     Population(1,:)=InitialValues;
60
61
62
63     for k=1:steps
64     %Calculate probabilities of each state change
65     p1=lambda*t;
66     p2=mu*Population(k,1)*t;
67     p3=K*Population(k,1)*Population(k,3)*t;
68     p4=Δ*Population(k,2)*t;
69     p5=p*Population(k,2)*t;
70     p6=c*Population(k,3)*t;
71     psum=(p1+p2+p3+p4+p5+p6);
72     p0=(1-psum)*t;
73
74
75     %Generate a uniform random number, scale it to the sum of probabilities
76
77
78
79
80
81         x=rand*psum;
82
83
84         %State change test
85
86         if x<p1 && x > 0
87             Population(k+1,:)=Population(k,:)+S1;
88         elseif x<p1+p2 && x > 0
89             Population(k+1,:)=Population(k,:)+S2;
90         elseif x<p1+p2+p3 && x > 0
91             Population(k+1,:)=Population(k,:)+S3;
92         elseif x<p1+p2+p3+p4 && x > 0
93             Population(k+1,:)=Population(k,:)+S4;
94         elseif x<p1+p2+p3+p4+p5 && x > 0
95             Population(k+1,:)=Population(k,:)+S5;
96         elseif x<p1+p2+p3+p4+p5+p6 && x > 0
97             Population(k+1,:)=Population(k,:)+S6;
98         else
99             Population(k+1,:)=Population(k,:)+S0;
100        end
101
102
103        %Setting the floor
104
105        %for j=1:3
106        %    if Population(k+1,j)<0
107        %        Population(k+1,j)=0;
108        %    end
109        %end
110
111
112
113
114    end
115
116
117    %Add end state population values to the average to compute the average
```

```
118      %later
119
120      Average=Average+Population;
121
122
123      %Create plots of T,I, and V against time
124      hold on
125      subplot(2,3,1), plot(time,Population(:,1))
126      hold on
127      subplot(2,3,2), plot(time,Population(:,2))
128      hold on
129      subplot(2,3,3), plot(time,Population(:,3))
130
131      %Store end values for display purposes
132
133      EndValues(trial,:)=Population(steps,:);
134
135  end
136
137
138  Average=Average/trials;
139
140  subplot(2,3,1), plot(time,Average(:,1),'r'), xlabel('Time'), ylabel('Healthy T-cells')
141  subplot(2,3,2), plot(time,Average(:,2),'r'), xlabel('Time'), ylabel('Infected T-cells')
142  subplot(2,3,3), plot(time,Average(:,3),'r'), xlabel('Time'), ylabel('Virus Particles')
143  subplot(2,3,4), hist(EndValues(:,1),100, title('Healthy T-Cell Quantity'))
144  subplot(2,3,5), hist(EndValues(:,2),100, title('Infected T-Cell Quantity'))
145  subplot(2,3,6), hist(EndValues(:,3),100, title('Virus Quantity'))
```

A.0.4. Stochastic Code.

Simulate and plot ODE with random valued IV:

```
function StochasticSimulator

clear
clc
clf

%We want to go from time t=0 to the end time, t=T. We want to do this in N
%steps of length L=T/N. This would be an iterative process. We start with the
%populations at time t=0. From there, we can calculate populations at time
%L by calculating EV, multiplying it by L and taking VAR, multiplying it by
%L, then multiplying that by a dW of unit length.  We would start with a
%matrix with three columns (for T, I, & V) and N+1 rows.


%Coefficients
lambda = .272;
mu = .00136;
k = .00027;
Δ = .33;
p=100;
c=2;

%Initial Values (T,I,V)
InitialValues=[200,0,4e-7];

R=(k*lambda*p)/(c*Δ*mu)

trials=2000;
T=60; %Total Time elapsed
N=600; % number of trials
dt=T/N;
time=[0:dt:T];
P=zeros(N+1,3);
Average=zeros(N+1,3);
EndValues=zeros(trials,3);
for trial=1:trials;
    P(1,:)=InitialValues;



    for i=1:N

        EV=[lambda-mu*P(i,1)-k*P(i,1)*P(i,3);k*P(i,1)*P(i,3)-Δ*P(i,2);p*P(i,2)-c*P(i,3)];
        VAR=[[lambda+mu*P(i,1)+k*P(i,1)*P(i,3), -k*P(i,1)*P(i,3), 0];[-k*P(i,1)*P(i,3), ...
            k*P(i,1)*P(i,3)+Δ*P(i,2),0];[0,0,p*P(i,2)+c*P(i,3)]];

        dW=[randn;randn;randn];
        dWt=dW*dt^(.5);
        %A=chol(VAR);
        A=(VAR)^.5;
        dP=EV*dt+(A)*dWt;
        P(i+1,:)=P(i,:)+[dP(1),dP(2),dP(3)];

        %Absorbant Boundrary Conditions
        %P(i+1, 1) = max( P(i + 1,1), eps) ;
```

```
55          %P(i+1, 2) = max( P(i + 1,2), 0) ;
56          %P(i+1, 3) = max( P(i + 1,3), 0) ;
57
58
59          %Reflective Boundrary Conditions
60          P(i+1, 1) = abs( P(i + 1,1)) ;
61          P(i+1, 2) = abs( P(i + 1,2)) ;
62          P(i+1, 3) = abs( P(i + 1,3)) ;
63
64      end
65
66
67
68
69      %EV=[lambda-mu*P(1)-k*P(1)*P(3);k*P(1)*P(3)-Δ*P(2);p*P(2)-c*P(3)];
70      %VAR=[[lambda-mu*P(1)-k*P(1)*P(3), -k*P(1)*P(3), 0];[-k*P(1)*P(3), ...
            k*P(1)*P(3)-Δ*P(2),0];[0,0,p*P(2)-c*P(3)]]
71
72      hold on
73      subplot(2,3,1), plot(time,P(:,1))
74      hold on
75      subplot(2,3,2), plot(time,P(:,2))
76      hold on
77      subplot(2,3,3), plot(time,P(:,3))
78      Average=Average+P;
79      EndValues(trial,:)=P(N+1,:);
80  end
81
82
83  Average=Average/trials;
84
85  subplot(2,3,1), plot(time,Average(:,1),'r'), xlabel('Time'), ylabel('Healthy T-cells')
86  subplot(2,3,2), plot(time,Average(:,2),'r'), xlabel('Time'), ylabel('Infected T-cells')
87  subplot(2,3,3), plot(time,Average(:,3),'r'), xlabel('Time'), ylabel('Virus Particles')
88  subplot(2,3,4), hist(EndValues(:,1),100, title('Healthy T-Cell Quantity'))
89  subplot(2,3,5), hist(EndValues(:,2),100, title('Infected T-Cell Quantity'))
90  subplot(2,3,6), hist(EndValues(:,3),100, title('Virus Quantity'))
```